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EDITED BY

HUGH THURSFIELD, D.M., F.R.C.P., and REGINALD MILLER, M.D., F.R.C.P.

WITH THE HELP OF

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THE LIFE HISTORY OF EPIDEMIC ENCEPHALITIS IN THE CHILD.*

By

MARY M. STEVENSON, M.A., M.D.,

(From the Medical Department, Royal Hospital for Sick Children, Glasgow.)

Many accounts of epidemic encephalitis have already appeared, but few relate specially to children, and fewer still give a survey of a large series of cases during childhood observed over a long period. It is, therefore, hoped that the present account of the life history of the disease in the infant and child will not be without interest.

From 1918, the first year in which epidemic encephalitis was observed in Glasgow, till the early months of 1927, eighty-three examples of the disease were seen in the Royal Hospital for Sick Children, Glasgow. The first three of these were described by Professor Findlay[1], in 1918; twenty-three were recorded in 1920 by Findlay and Shiskin[2]; and in 1923 the sequelæ as seen till 1921 in thirty-eight cases were described by Dr. Grace Anderson[3].

These eighty-three cases have been traced and followed as far as possible during the last three years. The general position at present is as follows: Twelve deaths have occurred: four of these in the acute stage. Eight cases cannot be traced. There are therefore sixty-three cases known personally to the writer at the present time (August, 1927). In accordance with the findings in other series, the onset was most commonly in the first half of the year. 70 per cent. of the cases were males. Age had apparently little influence since cases appeared in every year from birth to thirteen years, although the disease was relatively more frequent in children over seven years. The youngest case was aged two months at the onset and three others were under one year.

Apart from the possible exceptions about to be mentioned there is no evidence of case-to-case infection in this series. In 1924, in the month of April, four cases were admitted who attended one school and three who attended another school. These seven cases formed 63 per cent. of all the acute cases admitted during that epidemic. No two, however, were in the same class at school and there was no evidence that any of the children had been in immediate contact.

Course of Disease.

The course of the disease in these children has been fairly typical. No one case has presented all the symptoms observed. In the greater number, however, the picture when seen as a whole was characteristic. It was not always possible to diagnose the case with certainty in the acute stage, but the later stages when followed have made the diagnosis clear.

* Abstract of Thesis accepted for the degree of M.D., Glasgow University.

The course has, generally speaking, been as follows :—A child has suddenly become ill. Suddenness of onset has been very conspicuous in this series, being present in seventy-one of the eighty-three cases. Thus a child might go to school apparently normal and return two hours later extremely ill. The most frequent early symptoms were :—insomnia in 50 per cent, choreiform restlessness in 29 per cent, lethargy in 26 per cent, diplopia in 20·5 per cent, headache in 15 per cent, pain in 14 per cent. Other symptoms, such as vomiting, convulsions, etc., occurred much less often.

This sudden onset was followed by a period of acute illness which varied in length from a few days to two months. Fever was present for the first week or two ; the child was in some cases lethargic, in others wildly restless, or, it might be, restless for some days and then lethargic. Other symptoms such as respiratory disturbance, myoclonus, ocular disturbances, were also often present at this stage. On recovery from the acute illness there was usually a period of apparent return to health. This lasted from a few days to a month, but in every case was broken sooner or later by the appearance of new symptoms. The length of this latent period is evidently very variable : McAlpine[4] describes an adult case in which there had been apparently good health for more than three years.

In every case in this series this period of apparent recovery was broken by the appearance of one or other of the later symptoms. Mental changes, nocturnal excitement, conduct changes, respiratory disturbances, the Parkinsonian syndrome, loss of accommodation, choreiform restlessness, myoclonic movements and obesity occurred in that order of frequency, nocturnal excitement usually appearing first. Two or more of these might be present simultaneously or they might appear in sequence. No two cases presented these symptoms in exactly the same way. The individual picture is therefore varied but the general history is characteristic.

Signs and Symptoms.

Fever.

This was usually present in the early stage. Thirty-eight cases were admitted to hospital in the first two weeks after onset, and of these thirty-one showed a rise of temperature. The remaining seven were admitted from nine days to two weeks after the onset. These may, therefore, have already passed through a febrile period, as the duration of fever is frequently only a week or less.

Table I shows the duration of fever in the cases which survived.

TABLE I.

DURATION OF FEVER IN SURVIVING CASES.

Duration.	Cases.
1 week	8
12 weeks	11
23 ,, ...	6
36 ,, ...	2

The return to normal temperature was in every case earlier than the disappearance of other signs and symptoms: lethargy, for instance, commonly persisted for weeks after the disappearance of fever.

Except in fatal cases the temperature was never very high (Table II). In the four fatal cases the temperature before death was 101°, 102·6°, 104° and 108°. In one case followed by recovery the temperature rose to over 105° for some hours during a series of convulsions.

TABLE II.

MAXIMUM TEMPERATURES.

Temperature.	Cases.
99—100° Fahr.	3
100—101° ,, ...	3
101—102° ,, ...	4
102—103° ,, ...	10
103—104° ,, ...	7
104—105° ,, ...	2
105—106° ,, ...	1
108° Fahr.	1

Lethargy.

Lethargy was present in fifty of the eighty-three cases during the acute stage. In twenty-three it was the first symptom noticed. In twenty the lethargy followed a preliminary period of choreiform restlessness of from two to ten days. This type of onset with chorea appeared for the first time in 1920, and also occurred very frequently during the epidemic of 1924.

The lethargy in far the greater number of cases lasted from 10 to 23 days. The outstanding exceptions were two cases where it only lasted for 12 and 24 hours respectively, and four where it persisted for 9, 10, 14 and 16 weeks. These variations, however, did not appear to influence later developments.

The lethargy varied in depth in different cases and at different times in the same case. In some instances the child was never in bed, but slept whenever he sat down. As a rule, however, he lay completely impassive though able in most cases to respond to questions. The appearance often gave a false impression of paresis especially of the facial muscles. Occasionally a real though transient paralysis was detected. Lethargy at times deepened into coma. When this was accompanied by a rise of temperature death always followed. When lethargy had persisted for some weeks intermissions occasionally appeared. Thus in one case, after ten weeks of lethargy, a distinct improvement appeared for two days, and was followed by six weeks' of drowsiness, not so deep as before.

Lethargy accompanied by fever has not been seen in the late stages. In two cases, however, there have been long periods of lethargy accompanied by obesity. In one both symptoms disappeared after about 18 months; in the other, both are still present four years after the onset of the illness.

Disturbances of the Motor System.

Motor disturbances in this series can be classified thus: (1) Convulsions, only seen in the acute stage; (2) Choreiform restlessness, occurring both early and late; (3) Myoclonus, which appeared in both the early and late stages and has remained for years; (4) Parkinsonian syndrome, occurring in late stages only.

(1) Convulsions. The onset of the disease was marked by convulsions in two cases. In one other (Case 79) the child had a series of convulsions with a temperature of 104° on the fourth day of illness. This case later of the myoclonic type.

(2) Choreiform Restlessness. This was a very prominent feature in 39 cases. It was noted by Findlay and Shiskin[2] in 1920 and was found elsewhere at the same time. In 1924 it was a most characteristic feature of the epidemic.

The child suffering in this way is in a constant state of movement which ceases neither by night nor by day, and may indeed increase at night. Insomnia and a certain degree of delirium are present, though as a rule the child will answer questions fairly intelligently, and may even be able to control the movements for a moment or two.

In all but three cases, where it occurred first on the seventh day, this restlessness appeared as an early symptom. It lasted in most cases for from four to fourteen days, and in half the cases was followed by lethargy. In three atypical cases the chorea continued for one to two months, and in two others, where it was of a very violent description, it persisted for eighteen months and two years respectively, being accompanied by wild behaviour. Wimmer[5] believes that it is impossible in the early stages to differentiate between this restlessness and that of rheumatic chorea. In the present series, however, the history of a sudden onset, the presence of ocular symptoms or of fever, were found to be reliable points in diagnosis. The restlessness is usually of a more extreme type than is observed in rheumatic chorea and shows, in contrast to rheumatic chorea, a tendency to increase during the night.

The later stages of the disease are sometimes also marked by choreiform restlessness; not, however, of the extreme type seen in the early stages. It consists of such movements as shrugging the shoulders, touching surrounding objects, or running round the room. These can be stopped for a considerable time if the child's attention is gained, but he is apparently unable to remain quiet otherwise. In one case such movements started in one leg and arm a year after the onset of the illness but have in the last five years become generalized.

(3) Myoclonus. In 1920, both Walshe[6] and Sicard[7] reported cases which showed rhythmical contractions of the muscles. In the present series the first patient to show this symptom became ill in 1923. Altogether six examples of this type of the disease have been seen. Table III gives details of these:

TABLE III.
MYOCLONIC CASES.

Case No.	Year of acute illness.	Onset of Myoclonus.	Site.	Rate per minute.	Pain.	Hyperpnœa.	Present state of Myoclonus.	General condition.
52	1923	2nd week.	Respiratory.	44	Abdominal: general at onset.	Coinciding in rate.	Lessening.	Parkinsonianism improving.
69	1924	1st week.	Extraordinary muscles of respiration and arms.	48	At onset in arms.	ditto.	Lessening.	Hyperpnœa. Mentality very poor.
79	1925	1st week.	Respiratory muscles & diaphragm.	60	None.	ditto.	Lessening. Still strongly present in sleep.	Nocturnal excitement. Conduct very bad.
70	1924	4th week.	Right side of mouth and platysma.	60 to 80	None.	ditto.	Unchanged.	Parkinsonianism.
49	1923	24th month.	Left side of nose.	50	None.	Not coinciding.	Gone.	Conduct bad. Mentality very poor.
71	1924	19th month.	Right side of mouth.	44	None.	——	Marked. In series of 3 or 4 then slight pause.	Mentality poor.

The onset of myoclonus was in four of the six cases very early. In two it was one of the first signs observed. In all four it has persisted and has been as marked in the later stages as at the beginning. In another (Case 70) there was a variation from the usual course. This boy was admitted on the second day of illness in a state of choreiform excitement with a right-sided facial paresis. The paresis persisted till the fourth week, when a regular myoclonic twitch appeared in the same muscles. This remains after two years.

The sites of the myoclonic twitchings have been very similar, for three have affected the facial muscles and three the diaphragm and extraordinary muscles of respiration. The facial twitch in each case is unilateral. In the three cases where the respiratory muscles were affected it was and is strong enough to move the arms. In every case the twitch has remained confined to the original muscles affected.

The rate has been fairly constant in each case and has been peculiar to each. Thus in Case 70, quoted above, the contractions have been between 60 and 80 per minute for the last two years. In another (Case 71) the contractions occur in series of three or four and are about 40 per minute. This case and another (Case 49) where the contractions are not constantly present, are the two of late onset. Sleep has not lessened the contraction in any of these cases; in Case 79, indeed, the contraction which has now almost disappeared by day is still very definite during sleep.

Association with pain. Marie and Levy[9] mention cases in whom lancinating pain and fever at onset were succeeded by the appearance of short, rapid explosive muscular contractions.

In one of this series (Case 69) the child complained first of pain in the hands which made him cry out. This was followed in a few hours by regular contractions of the thorax and arms. On the next day he was admitted to hospital with fever and myoclonic contractions of the muscles of the thorax and arms, which persisted for two years.

When the contractions affect the abdominal muscles the presence of pain may make diagnosis difficult. Hinds Howell[10] reports a case which was diagnosed as appendicitis, and Stevenson[11] records three sent to the Glasgow Royal Infirmary as acute abdominal cases. In the present series one child (Case 52) complained suddenly in February, 1923 of severe pain in the wrist, arm and back and next day in the abdomen. For one week she was treated as a case of acute rheumatism, when the diagnosis was changed to appendicitis. She was then admitted to a surgical ward but was transferred to a medical ward two days later. Twitching movements were present with pain but a few days later these were seen to be myoclonic in character. Hyperpnœa appeared ten days later. Eight months after the onset of illness she was again sent to the surgical wards as a case of appendicitis and once more transferred to the medical wards. The myoclonic contractions now coincided with respiration. Fever was again present with pain. In April, 1924, she was for a third time sent to the hospital with the diagnosis of appendicitis. Since then her condition has improved.

In no case has myoclonus been present alone in the later stages: other symptoms have invariably been present.

Prognosis. Myoclonus has been in this series very persistent. In four cases it appeared in the acute stage and is still present after one, two and three years. In three of these it is now much less marked, in the fourth it is unchanged after two years. As regards the two cases where it appeared first in the late stages, it is still present in one, but disappeared in the other after being present for only a few months.

(4) Parkinsonian Syndrome. Kennedy[12] found that twenty-one out of fifty-nine children, seen by him on account of sequelæ, developed this syndrome. Of the seventy-three cases seen in the later stages of the illness in this series, twenty-two or 30·2 per cent. have shown some degree of Parkinsonianism. Fifty-five cases were seen in the first four months of illness and, of these, fourteen are now Parkinsonian in type.

Sex. Seventeen of the twenty-two children affected are boys.

Age. The ages at the time of the acute illness are seen in Table IV.

TABLE IV.

AGE-INCIDENCE IN PARKINSONIAN SYNDROME.

Age.	Total cases.	Parkinsonian cases.
Up to 3 years	10	1
3 to 6 years	18	4
6 „ 8 „	20	5
8 „ 10 „	11	5
10 „ 12 „	19	3
Over 12 years	5	4

Our figures do not support Hall's suggestion[8] that the syndrome appears more readily in the older patients.

Onset of the Parkinsonian Syndrome. Cases have been recorded by Hinds Howell[10], Buzzard[13] and others in which the syndrome appeared during the acute illness. This was never so in the present series. The period between recovery from the acute illness and the onset of Parkinsonianism was, however, in two cases very short. In neither of these was the normal animation fully recovered before the characteristic immobility became apparent, so that it is difficult to say when the syndrome really appeared. In a third, the first signs were also early, appearing three weeks after recovery from the acute illness. In six cases the period was between two and three years; and in one at least more than three years. These intervals were invariably bridged by the presence of other sequelæ.

Signs and Symptoms of the Parkinsonian Syndrome. Immobility of the face or of one limb was usually the earliest sign of the syndrome to be noticed. In all the twenty-two cases this has been present to some extent. In generalized cases the attitude is fixed and wooden in appearance. The child usually stands with the trunk bent forwards and elbows flexed. One child holds the trunk backwards, and two keep the head bent to one side with the trunk inclined towards the same side. The general appearance is in most cases unmistakeable. The gait is characteristic where the lower limbs are affected. The feet are hardly lifted from the ground, the steps are short. Well developed festination and retropulsion in this series are present, however, in only five cases.

As the syndrome advances, talipes equinovarus develops. This is present in all six of the most severe examples of the syndrome and in four of these it is bilateral. Some degree of slowness of movement is conspicuous in every case. In three of the older boys it is very pronounced. The phenomenon of sudden activity shown by an apparently immobile patient, named by Souques[14] "*kinesia paradoxa*," is present in four cases of the series. Cruchet[15] also describes such patients. The first child in whom this was observed in the present series is a boy who was acutely ill in 1920. He has since suffered from nocturnal excitement, hyperpnœa, and moral change, and is now a typical example of the Parkinsonian syndrome. His gait and attitude are in general remarkably wooden. On a sudden summons he has been seen by the present writer moving very rapidly, at a pace quite at variance with his usual extreme slowness.

Tremor has been present in eight of the twenty-two cases. In four of these, it is unilateral and is brought on by excitement or effort. After a moment it becomes of wide amplitude and irregular, and spreads to other limbs. In one case, in which the syndrome has now receded, the tremor was bilateral, increasing on effort, and much exaggerated at night. The third form of tremor affects all the limbs, is very fine and is constantly present. This is seen in two children.

Voice.—In the more pronounced cases the voice has become high in pitch and monotonous in tone. Articulation tends to become slurring. This may be partially due to facial immobility but certainly varies, usually becoming more pronounced in the evening. This increase of Parkinsonianism with fatigue is emphasized by Sainton and Schulmann.[16]

Excessive salivation was present in all but two of the Parkinsonian cases. These children are usually seen with the lower jaw hanging, and saliva dribbling out of the mouth. Excess of saliva is present also in other types but in these it is usually associated with the act of spitting. One child has continued this habit for five years.

Table V gives details of the twenty-two cases :—

TABLE V.

PARKINSONIAN CASES.

Case No.	Attitude.	Gait.	Speech.	Salivation	Tremor.	Previous sequelæ.	Other sequelæ now present.	General condition.
23	Typical	Festination and retropulsion. Double equino-varus.	High, slurring.	Excessive	Coarse.	Nocturnal restlessness. Obesity.	None.	Very weak.
12	,,	Double equino-varus.	,,	,,	,,	Nocturnal restlessness. Conductbad.	,,	,,
28	,,	Festination. Retropulsion.	,,	,,	,,	Hyperpnœa	,,	,,
68	,,	Slow. Unilateral equino-varus.	Slurring.	,,	,,	None.	,,	,,
72	,,	Very rigid.	Slow.	,,	None.	Chorea. Conduct bad.	,,	,,
80	,,	,, ,,	Slurring.	,,	Coarse.	Nocturnal restlessness.	,,	,,
18	,,	Rigid. Unilateral equino-varus.	,,	,,	,,	Noct. restlessness chorea.	,,	Can walk fairly well.
17	,,	Festination. Retropulsion.	High, slurring.	,,	,,	Nocturnal restlessness.	,,	,,
62	,,	Festination.	Slow.	Normal.	None.	Nocturnal restlessness and sniffing.	,,	,,

TABLE V—*continued.*

PARKINSONIAN CASES—*continued.*

Case.	Attitude.	Gait.	Speech.	Salivation	Tremor.	Previous sequelæ.	Other sequelæ now present.	General condition.
33	,,	Festination and retropulsion.	Slurring.	,,	,,	Nocturnal restlessness. Hyperpnœa.	Hyperpnœa.	,,
76	,,	Immobile. Drags one foot.	,,	,,	,,	Nocturnal restlessness.	None.	,,
36	,,	,, ,,	High, slurring.	,,	Fine.	Nocturnal restlessness. Conduct bad. Hyperpnœa.	,,	,,
75	,,	,, ,,	Good.	,,	None.	Nocturnal restlessness.	,,	,,
4	,,	Unaffected.	Slurring.	Excessive.	,,	Choreiform restlessness. Hyperpnœa.	Choreiform restlessness. Hyperpnœa.	Can walk well.
74	,,	Rigid.	High, Varies greatly.	Normal.	Fine.	Nocturnal restlessness.	None.	Deteriorating.
70	Head to one side.	,,	Slurring.	Excessive.	Coarse.	Nocturnal restlessness. Myoclonus. Conduct bad.	Myoclonus. Conduct bad.	,,
65	Immobile.	,,	Unaffected.	,,	None.	Nocturnal restlessness. Conduct bad.	Nocturnal restlessness. Conduct bad.	Deteriorating.
52	Typical.	Little affected.	Slurring, quick.	Normal.	,,	Myoclonus. Hyperpnœa. Conduct bad.	Hyperpnœa Myoclonus.	Improving.
11	,,	Immobile.	Indistinct	Excessive.	,,	Bad conduct.	Cruel. Violent.	Deteriorating
73	,,	Almost unaffected.	Very indistinct and slurring.	Very excessive.	Coarse at night.	Nocturnal restlessness. Conduct bad.	Bad conduct.	Very much better.
51	Slightly immobile.	,,	,,	Excessive.	None.	Nocturnal restlessness.	,,	Improving.
4	,,	,,	,,	,,	,,	Mentally deficient.	Mentally deficient.	,,

The face was in all cases masklike.

The greater number of those showing the most severe results have already passed through periods of bad behaviour, cruelty, filthy habits, etc.

Likeness to Progressive Lenticular Degeneration. The close resemblance between the picture of progressive lenticular degeneration and that of some of these cases is very striking. In four (Nos. 12, 17, 23 and 28) the general picture reminds one even more strongly of this disease than of paralysis agitans. The facial expression, vacant rather than mask-like, the open mouth, the facile smiles and depression which cross the face, the attitude in bed, the talipes equinovarus, and the high monotonous voice with the peculiar cry, are all extremely like to what is met with in Wilson's disease. The history of the acute illness in all, however, is typical of epidemic encephalitis and unlike lenticular degeneration : no case has presented any enlargement of the spleen. Rogers[17], Piltz[18], and Wimmer[5] have all remarked on the similarity of the two conditions and have reported illustrative cases.

Prognosis in the Parkinsonian Syndrome. There have been no deaths among the children who developed this syndrome. Nevertheless the prognosis for the child seems to be worse in this than in the other sequelæ. At the present date the condition of these children is as follows :—

Great improvement	One case.
Slight improvement	Two cases.
Stationary	Two cases, for two and three years respectively.
Deteriorating after stationary period	Three cases.
Steadily progressive	Fourteen cases.

Only three, or 14 per cent., have shown any signs of disappearance of the syndrome.

It appears impossible to find a relation between the early history of the case and the development of Parkinsonianism. One of the cases (No. 73) had a short acute illness of about fourteen days and almost a fortnight later the face, attitude and gait assumed a very immobile aspect. The condition progressed rapidly with coarse tremor, salivation and inarticulate speech, all most marked at night. A year later improvement began and the boy became practically free of the syndrome. He has since, however, been violent and extremely restless with persistent nocturnal excitement, and when seen at the date of writing is again showing rigidity of one leg with a tendency to retropulsion.

In all the other cases in which the syndrome appeared with so much severity, the condition has been progressive.

Cruchet[15] concludes that improvement, when it occurs, does so where the syndrome has been of early onset. In these cases he finds it fairly often curable. Case 73, just quoted, appeared to support this opinion but the re-appearance of rigidity contradicts it. Of the two who show slight improvement one, Case 52, presented none of the signs till ten months after the acute illness. In the other, the onset of the syndrome cannot be accurately timed. Two of the worst cases (Nos. 68 and 72) showed the first signs very early and have

been rapidly progressive. Of the six who are now bedridden, the period between the acute illness and the onset of the syndrome varied between five months and two years.

Ocular Signs and Symptoms.

Since the first report of this disease by Economo[19] in 1917, ocular signs and symptoms have featured in all clinical records. Foster Moore[20] found ocular paralyses in 75 per cent. of a series of ninety-seven cases.

In the present series, out of forty acute cases seen, twenty-nine or 74·5 per cent. showed some paralysis of the eye. For the greater part these paralyses appeared in the acute stage and were characterized, like the other paralyses met with in the disease, by their transient nature. The striking exception to this has been in paralysis of accommodation, which once being present has tended to remain and has often been a valuable aid in the diagnosis of a case coming under observation for the first time during the later stages of the disease.

Diplopia was complained of in nineteen cases, of which details are given in Table VI.

TABLE VI.

INCIDENCE OF DIPLOPIA.

Number of cases.	Day of illness.	Duration.
14	1st	8 lasted some hours. 3 lasted about 2 days. 2 „ „ 4 „ 1 „ „ 14 „
2	2nd	1 lasted about 1 day. 1 „ „ 6 days.
1	3rd	A few hours.
1	5th	About 2 days.
1	5th month	About 2 days.

In one case (No. 23) diplopia recurred after some days. It followed on fifteen hours of amaurosis, and persisted for several days.

Except for one case in which it appeared in the fifth month, none of the children has ever complained of it in the later stages. It is interesting to note that in all cases where diplopia occurred it was followed by a period of excitement of varying duration.

Strabismus was present in eleven cases during the acute stage, usually in very transient form.

Ptosis was only found in eight cases, and in three of these was bilateral. This figure is low as compared with that of the Ministry of Health Report[21] in which about half of the cases were stated to have been affected. In one of our cases ptosis persisted for several months,

Nystagmus occurred in six cases during the acute stage and has been found occasionally in the later stages also.

Internal muscles of the eye. In eighteen of the eighty-four cases loss of the reflex on accommodation with retention of the light reflex has occurred. In one other case accommodation has been sluggish. The following table gives the history of this paralysis in the cases in which it occurred.

TABLE VII.
REACTION ON ACCOMMODATION.

Case No.	Onset of illness.	Accommodation during the acute stage.	Accommodation after				
			1 year.	2 years.	3 years.	4 years.	5 years.
9	1918	Lost 3rd week.	Present.	...	...	...	Present.
11	1920	Child not seen.	Lost.	Lost.	...	...	Not traced.
12	,,	Child not seen.	...	Lost.	...	...	Lost.
17	,,	Present.	Sluggish.	Lost.	...	...	...
32	,,	Present.	Lost.	...	...	...	...
35	,,	Present.	Lost.	...	...	...	Not traced.
37	,,	Present.	...	...	Lost.	...	Lost.
36	,,	Lost.	...	...	...	...	Lost.
21	,,	Lost.	Lost.	Lost.	...	Lost.	Lost.
41	1922	Child not seen.	...	...	Lost.	...	...
42	1923	Sluggish.	...	Lost.	...	...	...
44	,,	Child not seen.	Lost.	Lost.	...	...	...
49	,,	Lost 2nd week.	Lost.	...	Lost.	...	...
52	,,	Lost.	Present.	Present.	Present.	...	...
62	1924	Child not seen.	Lost.	...	...	...	...
65	,,	Child not seen.	Lost.	...	...	...	...
75	,,	Child not seen.	Lost.	...	...	...	...
79	1925	Sluggish.	Sluggish.	...	...	...	...

It will be noticed that the reflex has returned in two cases. In both of these it was absent only for a short period during the acute stage. In all the others the condition has remained unchanged.

Boveri[22] lays much stress on loss of accommodation with retention of the light reflex in this disease and considers it one of the last manifestations to disappear. Genet[37] and Wimmer[5] also regard it as an important diagnostic aid in cases seen long after the acute onset.

The Argyll-Robertson pupil was not seen in this series, except for a short time in Case No. 16.

Inequality of the pupils was present in four cases during the acute stage. All, after one, two and five years, are now normal. Seven cases first seen in the later stages had unequal pupils. Of these, four are now normal five years after their acute illness, and three are still unequal one, one and a half and five years afterwards.

Fundi. Changes are recorded by different writers. In the present series such changes are rather more than usually frequent: in most instances the results of the ophthalmological examination was confirmed by Dr. Maitland Ramsay.

In acute stages. Thirty-four of our forty acute cases were examined ophthalmoscopically. Twenty-one were normal. The findings in the other cases are shown in Table VIII :—

TABLE VIII.
FUNDI IN ACUTE STAGE.

Case No.	Ophthalmoscopic appearances.
Case 3	"Discs slightly red and swollen—vessels engorged and tortuous."
Case 2	"Fulness of both discs with obscuration of the margins."
Case 23	"Both fundi red and swollen with vessels obscured in places."
Case 47	"Right disc distinctly pink."
Case 56	"Both discs congested—vessels full—margins obscured but slight cupping in centre—left disk greyish in colour."
Case 49	1st week, "nil." 2nd week, "Pink discs—congested veins, whole fundus red."
Case 51	"Pink discs and congested retinal veins. No sign of exudate in or around disc."
Case 54	"Both optic discs pink in colour, but well defined. Veins turgid with greatly increased calibre as compared with the arteries."
Case 53	"Both discs slightly swollen." Week later, "nil."
Case 74	"General appearance of right fundus is considerably more congested than that of the left. The appearance of the right is that associated with encephalitis."
Case 71	"Increased tortuousity of retinal veins in left eye as compared with the right. Otherwise the fundi are normal."
Case 67	"Discs red and slightly full. Margins obscured."
Case 78	"General hyperæmia."

In later stages. Thirty cases were examined two months or longer after the acute stage. Of these twenty-two were normal: the abnormal conditions in the remainder are shown in Table IX.

TABLE IX.
FUNDI IN LATE STAGE.

Case No.	Interval.	Ophthalmoscopic appearances.
Case 15	3 months	"Congestion of fundi of both eyes but nothing abnormal in the disc."
Case 23	3 months	"Veins enlarged. Slight swelling of discs."
Case 16	6 months	"Fundus in both eyes is abnormally red in colour. The optic discs are congested, and the red colour of the disc merges with the general red of the fundus so that its outline is obscured. The retinal veins are swollen and the light reflex is absent."
Case 63	8 months	"Right disc slightly swollen on temporal side, otherwise nil."
Case 12	9 months	"Discs well defined. Fundi unduly red."
Case 38	1 year ...	"Discs very pale—vessels small—optic atrophy." Died six days later.
Case 45	1 year ...	"Discs are congested but both congenital cup and margins are well defined. Veins are greatly congested and the calibre of the arteries is increased."
Case 19	$2\frac{2}{3}$ years	"General hyperæmia of whole fundus more marked on left side than on the right. Veins congested."

Paralysis.

The most frequent paralysis seen, after those of the eye, was that of the seventh cranial nerve. This occurred in seven of the thirty-eight cases and was always transient.

In six cases there were transient paralyses of the limbs. In one, however, a definite hemiplegia developed after recovery from lethargy, in the fifth week of illness. This persisted till death, which took place during the eleventh week of illness.

One child still shows a paralysis affecting the lower right half of the face. This developed about a year after the onset of illness and still persists after five years.

Reflexes.

The knee-jerks were increased in the majority of cases in both the early and late stages. Ankle clonus was present in four cases during the acute stage and in one during the later stages. An extensor plantar response was present in four cases during the acute stage. In three it was transient: in one it remained till death. In two cases, both of the Parkinsonian type, the extensor response appeared first during the later stages.

Pain.

In twenty-three cases pain of a severe neuralgic character was present during the early stages of the disease. In ten of these the pain took the form of headache, in nine it was situated in the limbs, in six in the abdomen and in one in the nose.

In most cases the site of the pain varied from day to day and physical examination revealed nothing abnormal. In the early stages sometimes caused difficulty in the differentiation of encephalitis from rheumatic fever and acute abdominal conditions (cf. Case 52, quoted above). In each case of headache in the early stages, lethargy followed. Pain in the other situations was always followed by some form of hyperkinesis.

Pain in the later stages has only been noted in four cases. In one it was followed by hemiplegia and death; in another by slight atrophy of the affected muscles; in the third a flitting pain was frequently present in the muscles of the limbs for about two years.

Cerebro-spinal fluid.

In sixty-seven cases the cerebro-spinal fluid was examined. In 1920 Prof. Findlay and Dr. Shiskin[2] gave a full report of twenty-four of these. Since then the examination has been continued in the same way, and the following remarks apply to the total number.

The fluid in the majority of cases was under increased pressure and clear; in one or two cases, not included here, it was blood-stained. Pandy's test was invariably negative.

Cytological examination usually showed a slight increase in the number of cells during the acute stage, estimating five cells per c.mm. as the maximum normal figure. During the first three months the figures 30, 20, 10 were common, although in one case during the tenth week only two cells were found. Increase in cells was also found by Boveri[23] and Symonds[24], the latter of whom found a number varying up to 50 or even 100. In the later stages the number of cells was normal except in two cases, where at the end of one year the cells numbered seven per c.mm. The increase in cells was found in every case to be due to an increase of lymphocytes.

Since 1920, the colloidal gold test of Lange has been carried out as a routine on these fluids. The results of seventy-five tests on sixty children are shown in Table X.

TABLE X.

COLLOIDAL GOLD TESTS.

39 Cases in acute stage ...	Positive in	21	52%	73%
	Faintly positive in ...	8	21%	
	Negative in	10	26%	
26 Cases between 2 months and 1 year after onset ...	Positive in	12	42%	71%
	Faintly positive in ...	7	29%	
	Negative in	7	29%	
9 Cases between 1 and 3 years after onset	Positive in	1	11%	33%
	Faintly positive in ...	2	22%	
	Negative in	6	66%	

The cases in whom we had the opportunity to repeat the test gave the following results :—

TABLE XI.

COLLOIDAL GOLD RESTS REPEATED AT INTERVALS.

Case No.	Period of illness.	Colloidal gold test.	Remarks.
38	1st week	000000000000	Died in 13th month.
	3rd week	555554320000	
32	2nd week	112322000000	Parkinsonianism.
	4th week	012210000000	
	3rd month	123310000000	
37	2nd week	012110000000	Mentally defective.
	3 years	000000000000	
31	3rd week	011211000000	Mentally defective.
	9th week	122211000000	
52	2nd week	000000000000	Parkinsonianism.
	4th week	234443100000	
51	1st week	012321000000	Mentally very poor.
	13th week	122232100000	
68	1st week	000000000000	Parkinsonianism.
	13th week	223410000000	
	1 year	001210000000	
72	2nd week	013554200000	Parkinsonianism.
	17th week	012322100000	

The test is therefore usually positive during the acute stage, although during the first week it is occasionally negative. After the acute stage is past it again becomes negative. This test is undoubtedly valuable when positive during the earlier months of the disease, but may be negative even when clinical signs are very striking. The Wassermann test in all the cases cited was negative.

The fluid was cultured in about one-third of the cases. A growth of Gram-negative diplococci was obtained in one, but in that fluid contamination was suspected,

Nocturnal Excitement.

Nocturnal excitement has assumed a very prominent position in the sequelæ seen in this series. Findlay and Shiskin[2], and later Anderson[3], described it in detail and since then it has been mentioned by all observers dealing with children. Kennedy[12], for example, found it in nineteen out of twenty-one children. In the present series, sixty-one out of seventy-three cases seen in the later stages suffered from it.

The course of events is now well known. As evening approaches, the child becomes more and more talkative and noisy, occasionally even violent. Other sequelæ which may be simultaneously present, e.g., hyperpnœa, become more marked during the wakeful hours. Almost invariably the child is anxious to sleep and tries by every arrangement of the bed to encompass this end, but without effect, until at about 5 or 6 a.m. he falls asleep and remains so till the next afternoon.

The inversion of the sleep rhythm in the present series usually followed on fairly rapidly, recovery from the acute illness. The average time from the onset of the acute illness was about ten weeks, though occasionally it appeared in the third week of illness, and in one case was delayed until three years afterwards. In four cases nocturnal excitement with sleep by day was the first sign of illness noticed (Table XII).

TABLE XII.

CASES IN WHICH INVERSION OF THE SLEEP RHYTHM WAS THE FIRST SIGN.

Case No.	Duration of N.R.	Present condition.
14	2½ years	Very backward. Mental ratio 57.
44	2½ years	Hyperpnœa, loss of accommodation, mentally backward. Mental ratio 67.
47	2½ years	Nocturnal restlessness still present. Bad tempered, quarrelsome. Mental ratio 89.
43	1½ years	Choreiform restlessness, mentally backward. Mental ratio 80.

In these four cases there was no history of an acute attack. In one or two others, however, further investigation of the history disclosed facts suggestive of an acute onset. Thus, in one case, the child was found to have been operated on for appendicitis two months earlier: on enquiry it was discovered that operation had not shown definite inflammation of the appendix and that the boy had been very drowsy during the illness. It seems probable that this was one of those cases with abdominal pain as an early symptom. In another an illness three months earlier, showing drowsiness and fever, had been diagnosed as pneumonia. Judging from the difficulty in obtaining these facts, it seems probable that in the other cases a slight preliminary illness may have been overlooked.

The psychic element in night restlessness is very evident. Change of surroundings frequently produces normal sleep for a night or two, even a change from one ward to another having this effect. Dr. Anderson found injections of sterile water successful in one case until the patient discovered the nature of the fluid injected.

The onset of fever restores the normal sleep rhythm. This was observed during intercurrent febrile attacks (measles and mumps). In two cases the present writer injected vaccine intravenously. Normal sleep accompanied the subsequent fever but reverted to the abnormal rhythm at once on its disappearance.

TABLE XIII.

RESPIRATORY DISTURBANCES.

Case.	Original respiratory abnormality.	Period at which disturbance appeared.	Duration since onset of disturbance to present.	State of respiratory abnormalities at present.
8	Panting attacks ...	2nd year	5 years	Present occasionally.
10	Panting attacks ...	4th week	6 years	Present less frequent.
11	Panting attacks ...	3rd year	3½ years	Present occasionally.
13	Panting attacks ...	7th month	5 years	Gone.
14	Panting attacks ...	3rd year	4 years	Gone.
16	Sighing, smacking lips.	2nd year	4 years	Gone.
19	Panting attacks ...	6th week	5 years	Less frequent.
20	Panting attacks ...	2nd year	4 years	Gone.
21	Panting attacks ... Clearing throat	3rd year	4½ years	Present.
24	Grunting noises ...	2nd year	Not traced	——
25	Panting attacks ... Blowing down nose	2nd year	4½ years	Gone.
28	Panting attaeks ...	14th month	4½ years	Gone.
29	Panting attacks ...	2nd year	4 years	Less frequent.
32	Panting attacks ...	3rd year	Not traced	——
33	Panting attacks ...	2nd year	4 years	Unchanged.
36	Panting attacks ...	3rd year	3 years	Improving.
40	Panting attacks ...	3rd month	Not traced	——
41	Panting attacks ... Apnœa ...	1st year	2 years	Present.
44	Panting attacks ...	2nd year	1 year	Occasional.
46	Panting attacks ...	1st year	2 years	Unchanged.
49	Continual rapid res-... piration. Panting attacks	Acute attack	2½ years	Present.
52	Continual rapid res-... piration. Panting attacks	2nd week	2½ years	Present, improving. Myoclonus of resp. muscles.
57	Panting attacks ...	1st year	2 years	Occasional.
59	Blowing nose, sniffing.	3rd month	1½ years	Present.
60	Panting attacks ...	2nd month	1½ years	Present. Apnœa now present. Violent conduct during attacks.
62	Sniffing, blowing nose.	1st month	1½ years	Present.
67	Panting attacks ...	1st year	1 year	Present.
69	Continuous rapid... respiration. Panting attacks	2nd week	1½ years	Present. Myoclonus of resp. muscles.
79	Panting attacks ...	1st month	—	Present.

Duration. The duration of this nocturnal excitement with sleep by day varied in this series from one month to five years. The average duration was about eighteen months.

This is not one of the most permanent sequels but it is one of the most difficult to manage, either at home or in hospital.

Disturbances of Respiration.

Disturbances of respiration form one of the sequels found by practically all observers of this disease. Goodheart and Cottrell[25], Levy[26] and others describe a respiratory type of the disease. Kennedy[12] found such disturbances in twenty out of fifty-one cases, Levy[26] in ten out of one hundred and twenty-nine, Hinds Howell[27] in three out of twenty-eight. In the present series these changes have been present in twenty-nine of the seventy-three cases seen in the later stages. Details of these are given in Table XIII.

In considering these cases, the classification used by Marie, Binet and Levy[28] has been used. These observers divided the disturbances into three classes :—

(*a*) Respiratory troubles properly speaking.
(*b*) Phenomena of spasmodic cough.
(*c*) Manifestations of the nature of respiratory tics.

In the present series, there have been no cases suffering from spasmodic cough but of the twenty-nine cases, twenty-three belong wholly to the first class, two to the third and three have shown manifestations of both.

Derangements of respiration which occurred in the present series are as follow : (1)Attacks of rapid and noisy breathing ; (2) Continuous rapid breathing with occasional attacks of noisy respiration ; (3) Apnœa. To these Marie, Binet and Levy[28] add bradypnœa, which they found in one case. Wimmer[5] found that this occurred seldom and in the present series it has never been observed.

(1) Attacks of rapid and noisy breathing form the most common respiratory disturbance and may appear hourly. They begin without warning and with no apparent cause. If the child is suffering from night restlessness, the attacks are much more frequent and severe by night. If sleep is normal, excitement of any kind appears to encourage an attack.

In all cases but one the children showed little disturbance during the attack, though one or two seemed restless while it lasted. The exception is formed by a boy of 10 years of age (Case 60) who between attacks is a quiet child and is becoming more and more passive in his general behaviour. About every 20 or 30 minutes rapid noisy respiration begins without any warning. It is accompanied by very violent behaviour in which he may break windows, tear clothing, or rush wildly out of any place or vehicle in which he may be. After some minutes there is a period of apnœa which lasts for about a minute. In this his face becomes blue, and latterly conscious is lost. He then resumes his former normal appearance and behaviour. He is very intelligent and has a mental ratio of 102, but owing to the violence of his behaviour cannot be kept at school. This coincidence of violence or hyperkinesis with

the disturbance of respiration was present in the majority of Kennedy's[12] series and is considered by him very characteristic. In our series, however, the case mentioned is the single example and he has only developed it within the last eighteen months.

(2) Only four cases (Nos. 49, 52, 69, 79) have shown a continuous increase in the respiration rate. In these it maintained a rate of 40 to 60 a minute. In two it is still present after periods of one and a half and two years. It appears to cause little or no inconvenience to the children though in one (No. 49) it causes speech to be staccato and indistinct. In the other three it might easily pass unobserved. In one (No. 52) this rate was originally broken by attacks of noisy breathing. These have now, after two and a half years, disappeared and the rate of the respiration has fallen almost to normal.

In one case (No. 49) after three months of continuous hyperpnœa, with a respiration-rate of 50 to 80 per minute, there developed a tendency to tetany as shown by facial irritability, cyanosis and a fall in blood calcium.

In three cases (Nos. 52, 69 and 79) respiration corresponded with a myoclonic twitch of the diaphragm and extraordinary muscles of respiration.

(3) Periods of apnœa occurred in two cases, always at the end of an attack of noisy breathing. One (Case 60) has been quoted above. The other (Case 41) is a marked example of the Parkinsonian syndrome. The hyperpnoeic attacks occur almost every half hour and are very frequent during examination. At the end of each there is a period of about half a minute during which the child does not breathe and the face becomes extremely cyanosed. She responds faintly to requests during this period, which is ended by a cough and return to her usual appearance and behaviour.

Respiratory tics, such as a constant clearing of the throat, nose-blowing and sniffing, are present in several cases and like many of the other signs in the disease are most marked by night. One boy, aged 10 years (Case 59), was in hospital for months suffering from nocturnal restlessness which followed immediately upon the acute illness. During the whole of his stay, he blew his nose and sniffed loudly almost without cessation from about 5 p.m. till 4 or 5 a.m. His recovery appears at present to be exceedingly good, but after two years he still sniffs very frequently.

The onset of the respiratory disturbance occurred in eight cases during the first two months of illness. In twenty-one it appeared after intervals of from three months to three years. In the majority of cases it has therefore been a late manifestation. The duration was always long in this series, the shortest period being two and a half years. In one case the disturbance still remains after six years.

Prognosis. The tendency of these respiratory abnormalities appears to be towards disappearance. Three of the twenty-nine cases cannot be traced, but of the remaining twenty-six respiration is now normal in six, and improved in ten. Of the ten unchanged, the onset of illness in six was in the years 1924-25, so that they are still recent. In some of the cases in which the disturbance has disappeared it existed in the most marked degree for long periods.

Mental changes in later stages.

Shrubsall[29] found, on examining London school children who had suffered from this disease, that the attention to school work and the value of the response steadily improved in most cases. This is very much more hopeful than the results in the present series of cases.

At the present time the mental state of the children in this series is, with only five exceptions, much below the average standard for their ages. It is extremely difficult to form an estimate of any value from ordinary observation. Parkinsonian cases from their expressionless faces and general slowness give an unduly bad impression, while many of the others from lack of natural shyness and reserve have an equally deceptive air of mental alertness. Both of these impressions are found on closer and longer observation to be erroneous.

In the effort to attain some definite idea of the mental capacity of children suffering from epidemic encephalitis, we were fortunate in having the assistance in the early cases of the late Dr. Watt and in the more recent years of Mr. Conn, from the Psychological Department of the University of Glasgow. The mental age and ratio were estimated by them while the children were in hospital. Mr. Conn has repeated the test in many of the children whom it has been possible to trace. The full results of these tests with further investigations have been published by Dawson and Conn[30]. Forty-six children of the series were tested and the mean of their mental ratio was found to be 87·73. The average intelligence of these was therefore significantly lower than that of nine hundred and seventy-four other hospital patients (90·53), and of their brothers and sisters (96·00). Thirty were re-tested at intervals varying from seven to thirty-six months, and the mean of their mental ratio was found to have dropped to 76·13. It was also found that the intelligence of the patients whose illness had lasted over twelve months was significantly lower than that of those whose illness was of shorter duration.

Hall[31], Paterson and Spence[32] and others believe that the younger the child at the time of the acute illness the greater is the degree of mental deficiency. That is certainly true in this series. Twenty were under five years at the onset of illness. Of these five have not been traced, two are apparently normal at present, nine are of very poor intelligence and four have died imbecile. In these very young children, affected before their mentality is developed much, arrest of development is necessarily particularly grave.

The results of mental tests show no difference between Parkinsonian cases, those who have shown changes in conduct, and the other varieties of the disease. All deteriorate equally. This is interesting since the general appearance in Parkinsonian cases and in those showing conduct changes is apt to give a wrong impression. One child in this series is, however, an exception. He is a boy who during attacks of hyperpnœa is most violent in conduct, but has a mental ratio of 102 and takes a good place in school.

Change in Conduct.

Many gradations of change in behaviour are present in this series. Some children, formerly docile, have become disobedient and unruly. Others have

most violent tendencies. The most common observation of the parents is that the child has "completely changed his nature." In this series forty-six out of the seventy-three cases seen in later stages showed a definite deterioration in conduct, shown as follows :—

Irritability, bad temper and violence ; Destructiveness ; Cruelty to children and animals ; Untruthfulness ; Dirty habits ; Thieving, and sexual precocity.

Of these the first four have been by far the most frequent.

In many of the children, sudden outbursts of temper are frequent ; in them they throw about dishes, knives, or anything within reach. Thieving has been common in five cases. In these, the thefts have been continual but never with intent to retain the stolen property. None makes any attempt to conceal the theft. All have been repeatedly punished by their parents with no effect. One, however, has now ceased the habit after a long time.

Many of the children become cruel. One boy cannot be left alone with his younger brothers for a moment on this account.

Details of these cases are contained in Table XIV.

TABLE XIV.

CHANGE OF CONDUCT.

Case.	Year of acute illness.	Change in behaviour.	Conduct at present.	Mental ratio.	General condition.
5	1918	Destructive, dirty, unmanageable.	Very good.	—	Very backward
7	1919	Violent temper, cruel.	Unchanged.	71	,, ,,
8	,,	Scratching, biting, vicious in temper.	Docile.	53	,, ,,
9	,,	Destructive, unmanageable.	Obedient, quiet.	—	,, ,,
10	,,	Vicious, destructive, violent.	Improved.	—	,, ,,
11	1920	Treacherous, cruel.	Unchanged.	—	Parkinsonian.
12	,,	Unmanageable, violent temper.	Much improved.	—	,,
13	,,	Destructive.	Improved.	74	Very backward.
14	,,	Destructive, violent temper.	Docile.	57	,, ,,
15	,,	Deceptive, violent, cruel, destructive.	—	—	Died of pulmonary tubercle.
18	,,	Disobedient, unmanageable.	Improved.	—	Parkinsonian.
20	,,	Emotional, dirty, morose, resentful.	Unchanged.	75	Very backward.
21	,,	Restless, bad temper, uncontrolled.	Unchanged.	63	,, ,,
23	,,	Irritable, emotional.	Much improved.	—	Parkinsonian.
24	,,	Violent, sexually precocious.	Worse.	—	Very backward.
25	,,	Bad tempered, uncontrolled.	Quite good.	—	? backward.
26	,,	Thieving, bad temper.	Improved.	—	Backward.
27	,,	Bad temper, unmanageable.	Not known.	—	—
28	,,	Quarrelsome, cruel, dirty.	Improved.	—	Parkinsonian.
29	,,	Destructive, vicious, dirty.	Improved.	—	Very backward. Hyperpnœa.
31	,,	Rude, cruel.	Improved.	56	Very backward.
32	,,	Cruel, destructive, thieving.	Not traced.	—	—
33	,,	Destructive.	Good.	—	Parkinsonian.
35	,,	Bad tempered, irritable and quarrelsome.	Not traced.	—	—
37	,,	Irritable, destructive.	Improved.	61	Very backward.

TABLE XIV—*continued.*
CHANGE OF CONDUCT—*continued.*

Case.	Year of acute illness.	Change in Behaviour.	Conduct at present.	Mental ratio.	General condition.
41	1922	Bad tempered.	Unchanged.	82	Parkinsonian. Hyperpnœa.
43	1923	Quarrelsome, bad tempered.	Improved.	80	Backward.
44	,,	Cruel, destructive.	Improved.	67	Very backward.
45	,,	Irritable.	Improved.	—	Obese, lethargic.
46	,,	Irritable, forgetful.	Unchanged.	—	Backward.
47	,,	Bad tempered, cruel.	Good.	93	Normal.
49	,,	Quarrelsome, unmanageable.	Unchanged.	77	Very backward. Myoclonus, hyperpnœa, accommodation lost.
51	,,	Wild, violent, throws weapons.	Worse.	73	Parkinsonian.
52	,,	Bad tempered, quarrelsome.	Improving.	87·5	Parkinsonian.
53	,,	Wild, rude, restless.	Unchanged.	—	Very backward.
57	,,	Untruthful, unmanageable, destructive.	Unchanged.	83	Restless and backward.
60	1924	Bad tempered, violent.	Worse.	102	Hyperpnœa.
61	,,	Irritable, bad tempered	Good.	89	Good.
65	,,	Steals, cruel, bad tempered.	Worse.	—	Good.
66	,,	Stealing, unmanageable.	Unchanged.	62	Choreiform restlessness.
70	,,	Bad tempered, violent.	Worse.	87·6	Parkinsonian. Myoclonus.
72	,,	Bad temper, cruel, quarrelsome.	Improved.	75	Parkinsonian.
73	,,	Bad temper, flings knives, spits.	Unchanged.	75	Parkinsonian. Improving.
75	,,	Bad tempered, cruel.	Unchanged.	84	Parkinsonian.
79	1925	Stealing, disobedient.	Worse.	—	Myoclonus. Hyperpnœa.
81	1926	Irritable.	Unchanged.	59	Restlessness. Choreiform.
83	,,	Cruel, destructive.	Unchanged.	—	Occasional nocturnal restlessness.

Apart from definite deterioration of character few children in the present series have been free of slighter changes. Almost all show an emotional reaction which was not present before, and few show normal shyness or reserve. In adult cases there appears to be frequently a continuously depressed attitude; this has occurred in one child only. She is morose and resentful when brought to hospital and is said to be unwilling to enter into the family life at home. In all the others friendliness and cheerfulness are very noticeable. They are always willing to express regret for their misdeeds and to promise improved behaviour, although this does not prevent early and frequent repetition.

Prognosis as regards conduct changes. Auden[33] found a gradual improvement in the behaviour and self-control of the larger number of his series of children, even where the conduct had been very bad. In the present series the prognosis as regards defects in behaviour is, on the whole, equally favourable.

The children whose acute illnesses occurred in the years 1918 to 1923 are, in the main, greatly improved in conduct, but there are still eight children, one dating back to 1919, whose behaviour is unchanged. In seven cases improvement in behaviour coincided with improvement in the time of sleep, and children who had been quite unmanageable became docile. In the majority, however, this had no effect. Where the acute illness was more recent, improvement is not so marked.

Children who are suffering from a progressive Parkinsonian syndrome are sometimes reported to be improving in behaviour. In these, motor incapacity rather than real improvement may be producing the change.

Obesity.

This has occurred as a late manifestation in two cases, both girls. One of these had suffered from an acute choreiform attack, in 1920, followed by night restlessness. A year later abnormal increase in weight was noticed at the same time as general immobility became apparent. Two years later she was very stout and lethargic, with the Parkinsonian syndrome well developed. She was not seen again till 1925 when she was found to be very emaciated and confined almost entirely to bed by extreme general immobility, tremor, festination and retropulsion which render walking impossible. Wimmer[5] reports a similiar case.

Other Systems.

Bradycardia was present in two cases during the acute stage. In both it occurred during a period of very deep lethargy. In one it remained for four days ; in the other for about two weeks. At the onset of the fall in the pulse rate in the second, the temperature rose to 102°, but the fever only lasted a few hours. *Constipation* was very severe in about 50 per cent. of the cases during the early weeks of illness. *Labial herpes* was present in the febrile stage in two cases. Filtz[18] saw it frequently at this stage, but it has not often been reported by other observers.

Prognosis in Epidemic Encephalitis.

The prognosis as regards life in children affected by this disease appears from this series to be fairly good. Only four, or 10 per cent., died during the acute stage. All these deaths occurred within the first sixteen days. Eight (10·5 per cent. of the children traced) died at varying periods after the acute illness. No one type of acute illness points in this series to a fatal result. The deaths during the acute stage occurred in two of the violently choreic type, in one of both chorea and lethargy, and in one purely lethargic case. A rectal temperature above 104° was certainly of bad omen. The ages of the patients in whom death occurred in the acute stage were from 9 to 11 years, at which ages the disease was commonest. Of the eight who died in the later stages, four were under 13 months when acutely ill. Sex does not appear to have influenced the mortality. Seven of the eleven children who died were males, the same proportion as in the entire series.

Prognosis as regards survivors. Shrubsall[29] in a series of 191 children found that 13·6 per cent. make complete recoveries, Robb[34] 5 per cent., Nonne[35] found few definite cures in 161 cases. Grossman[36], after intervals ranging up to 24 months, concluded that 70 per cent. had made good recoveries but on re-examination after intervals from one to three years found that only ten out of ninety-two cases were free of nervous symptoms.

In the present series sixty-five children are alive and have been examined recently. Of these only three are normal, both physically and mentally. One of the others, who was slow mentally and stunted in growth, has during the past year improved greatly and has recently been passed as suitable for the Territorial Force.

In no case was recovery from the acute stage permanent. This period was in all cases brought to an end by the appearance of one or other of the sequelæ. The three children who now appear normal after periods of one year, eighteen months and two years respectively, all suffered from periods of nocturnal excitement and irritability between the apparent recovery following on the acute illness and the present improvement. The length of these periods makes it at least hopeful that these may eventually make complete recoveries. The fact that two of these have now regained the normal mental ratio for their age is also of good omen.

Of the remaining cases, one boy mentioned above earns a little money but is now deteriorating; several are in institutions, being beyond home management, and five are constantly in bed. The others with few exceptions are either in special schools or reported as incurable.

The most serious and most frequently progressive and crippling of the later manifestations is the Parkinsonian syndrome but mental deterioration is almost equally progressive. The other sequelæ tend, on the whole, towards improvement.

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HEPATIC EFFICIENCY: THE VALUE OF THE HÆMOCLASTIC AND THE LÆVULOSE TESTS IN CHILDHOOD.

BY

MURIEL J. BROWN, M.B., Ch.B., D.P.H.

(From the Medical Department, Royal Hospital for Sick Children, Glasgow.)

The liver is so complex an organ and has so many functions to perform that no single test can serve as a true index of its efficiency. In consequence several tests have been devised for detecting hepatic disease. The van den Bergh test, and the phenol-tetrachlorphthalein test, are intended to give some indication of the state of the biliary activity of the liver; while the glycuronic acid test, and Widal's 'hæmoclastic crisis' have been regarded as of value in estimating the antitoxic function of the liver. For estimating the integrity of glycogenesis the lævulose test has been employed.

The present communication is based upon an investigation of the hæmoclastic crisis and the lævulose test in normal and abnormal conditions of childhood, and was undertaken to determine the value of these tests as indicating disease of the liver.

The 'Hæmoclastic Crisis' in Childhood.

This test, which is an application of the physiological digestion leucocytosis, was first employed by Widal[1] in 1920. It consists in determining the number of leucocytes in the blood after fasting, and also 10, 20, 40, and in some cases 60 minutes, after the ingestion of a standard meal (seven ounces of milk). Widal maintained that in health a leucocytosis is invariably obtained, but that when disease of the liver exists the post-prandial leucocytosis is replaced by a leucopenia. This varying reaction he interpreted as evidence of whether peptones are arrested in the liver or not, their presence in the systemic circulation inducing a leucopenia. Moutier and Rachet[2], however, have brought forward evidence that the phenomenon of "hæmoclasis" is the effect of a physical disturbance of the vasomotor system rather than a chemical reaction connected with the liver.

Some authors like Widal have considered this test as of great value in deciding whether the liver is healthy or not. Wilson[3] obtained a leucocytosis in thirty students after the ingestion of milk, a rise of 3,000 or upwards occurring after 20 minutes in more than half of the cases; only two of the subjects failed to show a rise of more than 1,000. In diseases of the liver, on the other hand, this author obtained an invariable fall. Shaw[4], on the contrary, performed the test in a large series of healthy individuals and also in cases of hepatic disease, and from his results totally discounts the value of the test as a means of estimating hepatic efficiency. Schiff and Stransky[5] obtained a leucopenia in all normal infants as well as in infants with disease of the liver. Misasi and Aiello[6] state that a leucopenia is normally induced in all children under 10 years of age, but that in digestive disturbances and congenital syphilis a leucocytosis may occur.

Tests in Normal Children.

The leucocytic changes were observed after the ingestion of milk in twenty normal children whose ages ranged from a few weeks to 12 years, and the results are shown in Table I. The amount of milk given varied according to the age of the child, the children under one year receiving an amount equal to their theoretical caloric requirements, while those over one year received 210 c.cm. of milk. In the adjudication of these results a change of less than 10 per cent has been considered within the limits of experimental error.

TABLE I.

THE LEUCOCYTE COUNT IN NORMAL CHILDREN AFTER THE INGESTION OF MILK.

Case No.	Age.	Leucocyte count.					% change in leucocyte count.
		Fasting.	Minutes after feed.				
			10	20	40	60	
1	15 wks.	11,000	9,400	8,500	13,200	—	—14% in 10 min. —22% in 20 min.
2	3 mths.	9,600	12,400	8,500	11,600	—	+28% in 10 min. —11% in 20 min.
3	4 mths.	9,800	7,400	8,600	9,600	—	—24% in 10 min. —12% in 20 min.
4	3 mths.	9,600	12,400	8,500	11,600	—	+29% in 10 min. —12% in 20 min.
5	1⅞ yrs.	12,000	13,600	12,400	11,200	12,500	+13% in 10 min.
6	2½ yrs.	14,000	12,600	13,800	13,600	14,200	—10% in 10 min.
7	3 yrs.	12,000	11,800	12,900	13,200	13,600	+10% in 40 min.
8	4½ yrs.	8,900	8,400	9,200	8,700	—	No effect.
9	4¾ yrs.	9,400	12,300	10,600	11,200	10,900	+30% in 10 min.
10	5 yrs.	9,400	8,800	7,800	9,200	10,400	—17% in 20 min.
11	5¾ yrs.	8,600	9,500	10,400	10,200	9,800	+21% in 20 min.
12	5 yrs.	10,200	12,400	11,600	10,800	—	+21% in 10 min.
13	6 yrs.	9,800	11,200	8,200	8,400	—	+14% in 10 min. —16% in 20 min.
14	7 yrs.	12,400	13,200	12,600	10,400	—	—32% in 40 min.
15	7 yrs.	12,300	14,000	13,600	12,000	—	+13% in 10 min.
16	8 yrs.	9,420	8,800	10,600	9,780	—	+10% in 20 min.
17	9 yrs.	10,240	12,400	11,200	9,400	—	+21% in 10 min.
18	10 yrs.	9,400	7,100	7,800	—	9,300	—24% in 10 min.
19	11 yrs.	8,600	7,800	9,420	8,400	—	No effect.
20	12 yrs.	7,600	9,240	8,800	9,400	—	+21% in 10 min.

Results.—A leucocytosis varying from 10 per cent. to 30 per cent. was obtained in 45 per cent. of the cases ; a leucopenia varying from 10 per cent. to 32 per cent. in 30 per cent. of the cases ; no change was found in 10 per cent., and a paradoxical result in 15 per cent. In the majority of the cases showing a leucopenia the maximum fall occurred within 10 minutes ; in only one case (No. 14) was the maximum fall not reached until 40 minutes after the ingestion of the milk. In none of the cases did a definite leucocytosis occur later. In the cases showing a post-prandial leucocytosis the maximum rise also occurred within 10 minutes. There was no apparent correlation between the age of the child and the leucocyte count obtained after the ingestion of the milk.

From these observations there is no evidence that in infancy or childhood the ingestion of milk produces a specific effect on the leucocyte count of the peripheral capillary blood, either in the direction of a leucopenia or a leucocytosis.

Tests in Abnormal Children.

In spite of the above conflicting results, however, an attempt was made to see if any consistent effect occurred when there was evidence of hepatic disease. Ten children suffering from unequivocal disease of the liver, and fifteen in whom there existed probable disease of the liver, were investigated. The results are given in Tables II and III.

TABLE II.

THE LEUCOCYTE COUNT AFTER THE INGESTION OF MILK IN CHILDREN WITH LIVER DISEASE.

Case No.	Disease.	Leucocyte count.					% change in leucocyte count.
		Fasting	Minutes after feed.				
			10	20	40	60	
1	Catarrh. jaundice	15,400	14,800	12,400	13,400	—	—19% in 20 mins.
2	,, ,, ,, ...	14,800	13,920	15,400	14,200	—	No effect.
3	,, ,, ,, ...	6,800	8,800	8,900	8,600	6,700	+29% in 20 mins.
11	Icterus neonat. ...	10,000	6,600	8,000	9,200	—	—34% in 10 mins.
14	Banti's disease ...	11,200	13,400	8,200	8,000	—	+19% in 10 mins. —44% in 40 mins.
16	,, ,, ...	11,250	15,937	10,312	10,000	10,937	+41% in 10 mins.
17	Hanot's disease	8,800	6,000	6,400	6,600	8,600	—32% in 10 mins.
18	Hodgkin's disease	8,900	7,250	6,300	7,600	9,750	—29% in 20 mins.
19	Congen. syphilis	10,600	11,200	10,800	10,400	—	No effect.
20	Multilobular cirrhosis	18,600	22,800	14,400	13,400	15,400	+40% in 10 mins. —34% in 40 mins.

Results.—It is seen from Table II, in which details of the results in definite hepatic disease are given, that in 40 per cent. of these cases a leucopenia varying in degree from 10 per cent. to 34 per cent. resulted, while in 20 per cent. a marked leucocytosis developed and in 20 per cent. no appreciable change was found.

TABLE III.
THE LEUCOCYTE COUNT AFTER THE INGESTION OF MILK IN CERTAIN PATHOLOGICAL CONDITIONS.

Case No.	Disease.	Leucocyte count.					% change in leucocyte count.
		Fasting.	Minutes after feed.				
			10	20	40	60	
24	Hodgkin's disease	3,800	4,000	3,800	3,700	—	No effect.
25	Congen. syphilis	12,400	12,900	12,600	12,800	—	No effect.
30	Gaucher's disease	7,600	9,800	11,600	8,000	7,600	+53% in 20 mins.
29	,, ,,	7,800	8,900	7,700	9,240	—	+19% in 40 mins.
31	,, ,,	6,000	6,800	5,800	5,800	6,200	No effect.
	,, ,,	6,900	7,000	7,200	8,400	6,600	+23% in 40 mins.
36	Coeliac disease (?)	6,400	7,800	8,200	5,300	5,800	+28% in 20 mins. —17% in 40 mins.
37	,, ,, (?)	10,400	9,260	10,820	11,880	—	—10% in 10 mins. +13% in 40 mins.
28	Wilson's disease	7,800	6,600	6,600	5,400	5,500	—30% in 40 mins.
29	,, ,,	7,200	7,400	7,400	7,000	7,200	No effect.
26	Acholuric jaundice	10,200	9,600	8,000	7,600	—	—25% in 40 mins.
27	,, ,,	37,000	22,600	23,800	18,400	17,400	—58% in 60 mins.
32	Gastroenteritis + ketosis ...	12,000	11,000	9,600	10,400	—	—20% in 20 mins.
34	,, ,,	11,200	11,600	12,800	11,600	—	+14% in 20 mins.
22	Hepatomegaly ...	9,600	12,000	11,600	9,340	—	+33% in 10 mins.
23	,, ...	6,600	4,400	4,200	5,800	—	—27% in 20 mins.

From Table III, where details of the test in cases of suspected and probable hepatic disease are given, the results are seen to be equally discordant.

Conclusion.

The hæmoclastic test in our hands has proved to be of no value in estimating the efficiency of the liver.

The Lævulose Test.

It is usually believed that lævulose after its absorption from the alimentary tract is carried by the portal system direct to the liver and there rapidly converted into glycogen and stored. Cathcart and Markowitz[7] state that lævulose cannot be oxidized by the tissues, and that it must first be converted into glucose by the liver before being deposited as glycogen. Hence the rationale of the test would seem to be that, in the absence of integrity of hepatic activity,

some of the lævulose ingested will filter through the liver and cause a rise in the blood sugar, and because of the inability of the tissues to utilize it there will ensue a delayed fall.

Straus[8] in 1901 was the first to draw attention to the different effects of the administration of lævulose and glucose. He regarded the presence of lævulose in the urine as evidence of impaired hepatic efficiency, because he found a lævulosuria after the ingestion of 100 grm. of lævulose in 90% of cases of liver disease, but in only 10% of normal cases. Schirokauer[9] in 1913 held that periodic examination of the percentage of sugar in the blood after the ingestion of lævulose was a more delicate method of detecting the ability of the liver to metabolize lævulose than its mere presence in the urine. He found that after the ingestion of lævulose in health there resulted practically no rise in the blood-sugar curve, whereas in subjects suffering from hepatic disease a definite rise occurred. Bergmark[10], as also Maclean and De Wesselow[11], and Folin and Berglund[12], shortly afterwards confirmed the finding of Schirokauer that in health the blood-sugar level was unaffected by the administration of lævulose. Spence and Brett[13] though concluding that this test affords a valuable means of estimating the actual degree of liver efficiency, hold that a rise in the blood-sugar content of 20 grm. may be obtained in the normal adult after the ingestion of 50 grm. of lævulose. Tallerman[14] also points out that the absence of any rise in the sugar curve is not as constant in health as had been supposed and that fairly wide variations do occur. Though he considers this test of value in estimating hepatic efficiency he holds that no conclusions can be drawn unless the rise exceeds 30 grm. He also drew attention to prolongation of the curve as strong evidence of some disorder of the liver. Cammidge, Forsyth and Howard[15], on the other hand, found in health a rise of as much as 50% in the blood-sugar content after the ingestion of lævulose. Frank and Melhorn[16] obtained in the normal child after the ingestion of 89 grm. of lævulose in 200 c.cm. of tea, a rapid rise in the blood-sugar with a slow irregular fall.

The possibility that these varying results may be due to variations in the purity of the lævulose employed in the test must not be lost sight of, and will be referred to later.

Method.—The technique employed for the lævulose test is the same as that for the glucose tolerance test. 1 grm. of lævulose per kgrm. of expected body weight was given to children under 12 years of age, and 50 grm. of lævulose to the few adult cases which were investigated. The percentage of sugar in the blood was estimated at half-hourly intervals after the ingestion of the lævulose.

Purity of the Lævulose.—The lævulose used throughout the tests was Merck's pure lævulose. Lævulose obtained from the British Drug House was also tried, but, as is seen from Table IV, the results obtained did not coincide, a higher rise being obtained with the B.D.H. lævulose than with Merck's lævulose.

TABLE IV.

THE BLOOD-SUGAR CONTENT AFTER "MERCK'S" LÆVULOSE AND "B.D.H." LÆVULOSE.

Case No.	Lævulose.	Percentage of sugar in the blood					% Increase in blood sugar.
		Fasting.	Hours after lævulose.				
			½	1	1½	2	
1	B.D.H. ...	·098	·125	·118	·106	·093	26
	Merck's ...	·090	·112	·106	·093	—	24
2	B.D.H. ...	·106	·143	·120	·106	—	34
	Merck's ...	·100	·125	·112	·100	·100	25
3	B.D.H. ...	·106	·134	·125	·100	—	26
	Merck's ...	·100	·108	·112	·100	—	12

Because of this discrepancy in the results with the two samples of lævulose Prof. Patterson submitted them to chemical analysis and found the specific rotation for sodium light of the Merck's specimen at a concentration of 10 and at a temperature of 22° C. to be —91·63; while the B.D.H. specimen gave a specific rotation of —82·49. This he concluded indicated an impurity in the B.D.H. lævulose of about 9 per cent. Hence the purity of the lævulose is a factor which should be taken into consideration in judging the normal rise in the blood sugar after the ingestion of lævulose, and a special standard must be set up for each type of lævulose used.

TABLE V.
THE SUGAR CONTENT OF THE BLOOD AFTER THE INGESTION OF LÆVULOSE IN NORMAL CHILDREN.

Case No.	Age.	Percentage of sugar in the blood				% Inc. in blood sugar.	Disease.
		Fasting.	Hours after lævulose.				
			½	1	1½		
1	7 yrs.	·098	·112	·096	·106	13	Conval. lobar pneum.
2	7 yrs.	·106	·098	·112	·100	5	,, ,,
3	5 yrs.	·086	·098	·106	·084	23	,, ,,
4	8 yrs.	·106	·112	·094	·100	5	,, ,,
5	9 yrs.	·108	·112	·098	·100	5	Conval. acute rheum. (no heart lesion).
6	8 yrs.	·086	·100	·098	·098	16	Epilepsy.
7	7 yrs.	·100	·094	·126	·100	26	,,
8	12 yrs.	·100	·112	·120	·100	20	,,
9	5 wks.	·100	·094	·100	·094	— 6	Incorrect feeding.
10	4 mths.	·075	·081	·096	·081	28	,, ,,
11	3 mths.	·088	·094	·100	·084	13	Dyspepsia. Vomiting stopped.
12	1½ yrs.	·100	·125	·112	·106	25	Unresolved pneum.
13	3 yrs.	·098	·088	·100	·100	—10	,, ,,
14	2 yrs.	·100	·120	·084	·106	20	Rickets.
15	5 yrs.	·084	·100	·106	·090	25	Conval. acute rheum. (no heart lesion).
16	10 yrs.	·098	·120	·125	·100	27	Epilespy.
17	3 mths.	·088	·094	·100	·084	14	Normal infant.
18	4 mths.	·094	·108	·094	·094	15	Incorrect feeding.
19	11 yrs.	·100	·125	·112	·098	25	Conval. acute rheum. (no heart lesion).
20	8 mths.	·081	·094	·100	·080	23	Incorrect feeding.
Average		·094	·104	·102	·096	15	

Results in Normal Children.

To obtain some idea of the comparative value of this test, its scope and limitations, twenty children who were recuperating from various diseases but in whom there was no suspicion or apparent evidence of disease of the liver were examined (using Merck's preparation of lævulose), and these have been taken as representing the normal. The results are shown in Table V.

A study of the figures obtained furnishes evidence that the average rise in the blood-sugar content is 10 mgrm., the highest being 27 mgrm. : in two cases a fall of 6 and 10 mgrm. respectively was obtained. Calculating the percentage increase, the greatest increase was 28 per cent. with an average of 15 per cent., an increase which is greater than can be allowed for by experimental error. In two of the cases examined no rise in the blood sugar was obtained, but, as previously mentioned, a fall of 6 mgrm. and 10 mgrm. respectively. In all the cases, except Nos. 10 and 15, the blood sugar had returned to the normal fasting level within one and a half hours after the ingestion of the lævulose. In these two cases the blood sugar was tending to fall, but, unfortunately, the result two hours after ingestion was not obtained. Age did not appear to have any effect on the height or duration of the rise.

For the purpose of comparison with the results obtained in pathological conditions we have taken as evidence of liver inefficiency an increase in the blood sugar of more than 30 per cent., and the presence of a prolonged curve, the blood sugar not returning to the normal fasting level within two hours.

Results in Pathological Conditions of Childhood.

The lævulose test was applied to a series of pathological conditions of childhood, and the results obtained are given in Table VI. For the purpose of better evaluation of the test the cases have been divided into three groups. In the first group of cases there was definite evidence of disease of the liver. In the second group there was probable disease of the liver, as evidenced by clinical examination ; and in the third group disease of the liver was merely problematical, no evidence of such being present on clinical examination, but the disease present suggesting a possible implication of the organ.

Group I.—Cases of Definite Disease of the Liver. In this series are—14 cases of catarrhal jaundice ; 5 cases of icterus neonatorum ; 1 case of multilobular cirrhosis of the liver ; 2 cases of Hodgkin's disease ; 2 cases of Banti's disease ; 1 case of fatty degeneration of the liver ; 1 case of congenital syphilis.

Catarrhal Jaundice.—In all, fourteen cases of catarrhal jaundice were investigated, six of them being children and eight adults. From a survey of the findings it will be seen that the rise in all the cases except three (Nos. 6, 12, and 13) was more marked than in the normal individual. In the majority of the cases the fall also was definitely delayed. In only five of the cases (Nos. 2, 4, 6, 12, and 13) did the blood sugar return to the normal fasting level within two hours of the ingestion of the lævulose.

In the children the increase in the blood sugar varied from 36 per cent. to 63 per cent., with the exception of one case (No. 6), where only a rise of 6 per

cent. was obtained. This very slight rise was obtained in a child in whom the jaundice had disappeared, and the only clinical evidence of disease of the liver at the time was enlargement of that organ. This child had had an attack of catarrhal jaundice two weeks before admission, when he was stated to have been jaundiced and to have passed high-coloured urine and pale motions.

Amongst the adult cases, which were all examined during the first week of illness, the same variations were found to occur, a slight fall being obtained in one case (No. 13), while another (No. 8) gave a rise of 85 per cent. with a definitely delayed fall. The test was repeated in the former case (No. 13) four and also eight days later, when the jaundice was more marked, and yet a negative curve was again obtained. The test was repeated after ten days in Cases 9 and 10, when the jaundice was fading but bile was still present in the urine. In both a normal curve was found, although a definite rise in the blood sugar with a prolonged fall had previously been obtained.

The extent of the rise did not appear to bear any relationship to the severity of the illness. The patient No. 4 appeared as ill as the patient No. 1, yet in the latter a rise of 59 per cent. with a prolongation of the curve was obtained, as compared with a rise of 36 per cent. and a return to the normal fasting level within $1\frac{1}{2}$ hours in the former.

Apart from Case No. 13 these results are in accordance with those obtained by Spence[7], who found a severe degree of liver inefficiency as evidenced by the lævulose tests during the early stage of catarrhal jaundice. In some cases, however, even before the jaundice had reached its height, a rapid recovery of the hepatic efficiency was indicated by a return to the normal behaviour of the blood sugar.

Icterus Neonatorum.—Icterus neonatorum occupies a peculiar place among examples of jaundice as many of the phenomena which are present in other forms of the disease are lacking. The distribution of the pigmentation differs from that in catarrhal jaundice, and there is an absence of clay-coloured fæces and of dissolved bile-pigments in the urine. Five cases of icterus neonatorum were examined. Three of these were found to give a positive result, the blood sugar increasing in two of the cases by 38 per cent. and in the other by 41 per cent. This increase, however, was not noted in two of the cases (Nos. 17 and 19) until two hours after the ingestion of the lævulose which probably indicated very slow absorption. Nevertheless the rise at the end of two hours points to definite liver impairment, and, although no distinct rise was obtained in the other two cases (Nos. 15 and 16), it is possible that absorption here may have taken place so slowly that the liver was able to deal with the very small amount of sugar which was carried to it at any one time.

Multilobular Cirrhosis of Liver.—The example of multilobular cirrhosis (No. 20) which was examined gave a positive result at a time when the only clinical evidence of hepatic disease was enlargement of that organ. Five months later yellowness of the skin and conjunctivæ, with the presence of urobilin in the urine, was noted, and on post-mortem examination the liver showed a distinct multilobular cirrhosis with here and there paler areas of "multinodular" hyperplasia.

Hodgkin's Disease.—Although this is not a true affection of the liver, Rolleston[18] states that the liver is involved in 50 per cent. of all examples of the disease coming to post-mortem examination.

Two cases of Hodgkin's disease were examined. One of these (No. 21) showed clinically only slight yellowness of the skin with the presence of urobilin in the urine, but on post-mortem examination the liver was found to be pale, deeply jaundiced and dotted throughout with firm whitish lesions. These areas on histological examination were found to consist of fibro-cellular tissue containing a fair number of large mononuclear cells and suggesting the appearance of lymphadenoma. In this case a rise of 37 per cent. was obtained in the blood sugar after the ingestion of lævulose with, however, a return to the normal fasting level within one and a half hours.

In the other case (No. 30) there was definite clinical evidence of impairment of the liver function as shown by an attack of jaundice six months before admission to hospital. When the case came under observation the liver was enlarged, and urobilin was present in the urine. A gland in the neck was excised and revealed the typical histological picture of lymphadenoma. In this case the lævulose test resulted in an increase in the blood sugar of 50 per cent., with a return to the normal fasting level within two hours.

Banti's Disease.—Two cases of so-called ' Banti's disease ' (splenic anæmia) were studied. They both showed progressive enlargement of the spleen, the presence of an anæmia of varying degree with a leucopenia, and free fluid in the abdomen, although in one case (No. 23) this was only noted at the time of the second examination. In both cases the diagnosis was confirmed by splenic puncture. Both gave positive lævulose tests. In one (No. 23) the percentage increase in the blood sugar at the time of the first examination was not more marked than that obtained in a normal child, but the return to the normal fasting level was delayed : this slow fall was again noted two weeks later, with, at this time, a more marked and definitely abnormal increase in the blood-sugar content.

Fatty Degeneration of the Liver.—An increase of 72 per cent. in the blood sugar and a delay in the return to the normal level after the ingestion of lævulose was obtained in one case (No. 24) which at post-mortem examination showed fatty changes in the liver.

Congenital Syphilis.—One case (No. 25) in which there was revealed at post-mortem examination syphilitic cirrhosis of the liver, reacted normally to lævulose. This is not in accordance with the findings of Duzar and Hensch[19] who obtained a positive lævulose test in all their cases of congenital syphilis.

Summary of Results in Group I.—If we summarize the results in the above 25 cases of certain liver disease, we find that 19 (76 per cent.) gave a definitely abnormal increase in the blood sugar after the ingestion of lævulose, and that of these 19 cases 15 (79 per cent.) also showed a delay in the return to the normal fasting level.

GROUP II.—CASES OF PROBABLE DISEASE OF THE LIVER. The second series consists of :—1 case of probable Banti's disease ; 3 cases of Gaucher's

disease ; 3 cases of Hanot's hypertrophic cirrhosis of the liver ; 1 case of passive congestion of the liver ; 2 cases of probable Wilson's disease.

Banti's Disease.—In this patient (No. 26) a negative lævulose test was obtained, though the clinical features suggested the diagnosis of Banti's disease. The spleen was palpable one finger-breadth below the costal margin, the liver four finger-breadths below the costal margin, and free fluid was present in the abdomen. There was a definite anæmia with a leucopenia, the white cell count numbering 4,685 per c.mm., and the fragility of the red cells was normal. The Wassermann reaction was negative. The child died three weeks after admission to the hospital, but unfortunately no post-mortem examination was obtained, and splenic puncture had not been performed.

Gaucher's Disease.—Splenomegaly of the Gaucher type is of particular interest because the pathogenesis is considered to be of the nature of an overgrowth of the reticulo-endothelial cells, with those in the liver also participating in the change. Three cases (Nos. 27, 28, and 29) were examined in which the spleen, on histological examination, after splenic puncture or splenectomy, showed the characteristic cells of Gaucher's disease. In all the cases the liver was enlarged : in the first two it was palpable two finger-breadths below the costal margin, and in the other case (No. 29) it was four finger-breadths below the costal margin. In none did the test in any way indicate impairment of the liver function, rises of only 21 per cent. 8 per cent., and 20 per cent. being obtained. In case No. 28 the lævulose test was repeated one month later, and a normal curve was again found.

Hypertrophic Cirrhosis of Liver.—Three cases diagnosed as possibly Hanot's disease on account of the enlarged liver were examined. In two (Nos. 31 and 32) a definite increase of the blood-sugar content was obtained with, however, a return to the normal fasting level within two hours. In the other case (No. 33), although the liver extended at the time of the test to the iliac crest the result was negative, but when repeated 9 months later there resulted a rise of 35 per cent., with a delay in return to the normal fasting level.

Cardiac Failure with Passive Congestion of the Liver.—In a case of severe valvular disease of the heart with cardiac failure and great enlargement of the liver and spleen, the liver extending $3\frac{1}{2}$ inches below the costal margin, the lævulose test was applied on two occasions and resulted in rises of the blood sugar of 43 per cent. and 42 per cent. respectively.

Progressive Lenticular Degeneration.—Two children, aged 12 and 10 years, in whom a clinical diagnosis of Wilson's disease (lenticular degeneration) was made, were examined. Although hepatic cirrhosis is found invariably post mortem in this disease, it is categorically stated by all recent writers that the cirrhosis is latent and gives no evidence (clinical or chemical) of its presence. In one of the cases (No. 36) there resulted a positive lævulose test in so far as the rise (35 per cent.) in the blood sugar was concerned, but the fasting level was reached within two hours. Neither example of the disease was confirmed by post-mortem examination, so that this result cannot be brought forward as a definite exception to the rule above mentioned.

Summary of Results in Group II.—In this group of cases of probable hepatic disease 6 (55 per cent.) gave a definite increase in the blood sugar after lævulose, and of these 6 cases, 2 (36 per cent.) also showed a prolongation of the curve.

Group III.—Cases of Problematical Disease of the Liver. The following cases are discussed under this group :—2 cases of acholuric jaundice; 4 of ketosis accompanying gastro-enteritis ; 3 of cœliac disease.

Acholuric Jaundice.—The jaundice in this disease is extra-hepatic in origin and no special pathological changes have been observed in the liver or bile passages.

Two typical examples of this disease with recurrent attacks of anæmia, enlarged spleen, and increased fragility of the red blood cells were tested. A negative curve was obtained in one (No. 37), but the other (No. 38) gave a rise in the blood sugar of 36 per cent., with a delayed fall. In both children splenectomy was performed. They were seen again one year later, and both appeared very well. The lævulose tests were repeated and negative curves were obtained.

Ketosis accompanying Gastro-enteritis.—The ketone bodies, β-hydroxybutyric acid, aceto-acetic acid and acetone, which are produced by the breaking down of one part of the fat bodies, are in the normal individual rapidly burned and broken up in the presence of sufficient glucose to maintain combustion into H_2O and CO_2. It has been suggested that, as a result of fever and toxæmia, the normal reserves of glycogen are depleted, and that the liver loses the power of producing glycogen. Thus there follows an insufficient supply of carbohydrates for the complete combustion of fat with a consequent ketosis. If this hypothesis be correct it would seem possible that in the presence of ketosis produced in this way, the damage to the liver might be revealed by the behaviour of the blood sugar after the administration of lævulose.

Tallerman[20] in twelve cases of ketosis accompanying infection found that only one gave a normal blood-sugar curve after the ingestion of lævulose. This he took as an indication of derangement of the carbohydrate metabolism due to hepatic inadequacy.

These results I was unable to confirm in the four cases (Nos. 39, 40, 41, and 42) of acute gastro-enteritis with ketosis which were submitted to the test. In all the cases there were vomiting, diarrhœa, and fever with signs of intoxication, and the presence of a considerable quantity of acetone in the urine. The maximum rise obtained in the blood sugar was 25 per cent., with in all cases a return to the normal fasting blood sugar level one and a half hours after the ingestion of the lævulose.

Cœliac Disease.—Some prominence has been given by certain workers to a disturbed function of the liver in this disease. Three cases (Nos. 43, 44, and 45) were examined, but a normal curve was obtained in all. In one a rise of 6 per cent. was obtained, while the other two only gave a rise of 8 per cent.

Summary of Results in Group III.—In the above group of examples of problematical hepatic disease it will be seen that on only one occasion (in a case of acholuric jaundice) was an abnormal curve obtained, and this case, when retested one year later, reacted normally.

TABLE VI.

THE SUGAR CONTENT OF THE BLOOD AFTER THE INGESTION OF LÆVULOSE IN VARIOUS PATHOLOGICAL CONDITIONS.

Case No.	Percentage of sugar in the blood.					% Increase in blood sugar.	Disease.
	Fasting.	Hours after lævulose.					
		½	1	1½	2		
Group I							
1	084	·134	·130	·125	·112	59	Catarrh. jaundice.
2	·093	·132	·108	·098	—	41	,, ,,
3	·100	·112	·154	·134	·125	54	,, ,,
4	·100	·136	·118	·090	·100	36	,, ,,
5	·098	·145	·160	·132	·112	63	,, ,,
6	·100	·108	·106	·100	—	6	,, ,,
7	·100	·165	·150	·134	·112	65	,, ,,
8	·084	·156	·134	·112	·125	85	,, ,,
9	·098	·134	·156	·156	·148	59	
10 days later	·100	·125	·125	·118	·100	25	,, ,,
10	·106	·168	·148	·152	·134	58	
10 days later.	·100	·112	·084	·092	—	12	,, ,,
11	·118	·156	·162	·137	·132	37	,, ,,
12	·106	·131	·125	·118	·100	23	,, ,,
13	·125	·118	·118	·118	—	—	
4 days later.	·125	·118	·125	·118	—	—	,, ,,
5 days later.	·118	·125	·118	·125	—	—	
14	·106	·156	·176	·150	·137	70	,, ,,
15	·130	·150	·125	·100	—	15	Icter. neonatorum
16	·086	·081	·093	·081	—	10	,, ,,
17	·081	·093	·093	·112	·112	38	,, ,,
18	·081	·112	·100	·081	—	38	,, ,,
19	·075	·075	·081	·100	·106	41	,, ,,
20	·100	·131	·118	·116	—	31	Multilob. cirrhosis.
21	·098	·135	·125	·096	·100	37	Hodgkin's disease.
Group II							
26	·112	·112	·108	·100	—	— 4	Banti's disease.
22	·134	·178	·162	·154	·150	32	,, ,,
23	·115	·140	·137	·125	·120	21	
2 weeks later.	·118	·143	·156	·131	·136	32	,, ,,
25	·064	·082	·075	·064	—	28	Cong. syph.
24	·081	·112	·150	·132	·112	72	Fatty degeneration.
27	·112	·112	·136	·106	·112	21	Gaucher's disease.
28	·100	·108	·100	·084	—	8	
1 mth. later.	·100	·106	·098	·086	—	6	,, ,,
29	·088	·076	·094	·106	·080	20	,, ,,
30	·112	·168	·156	·118	·106	50	Hodgkin's disease.
31	·081	·112	·137	·131	—	69	Hanot's disease.
32	·100	·137	·130	·100	·100	37	,, ,,
33	·112	·125	·114	·112	·112	20	
9 mths. later.	·112	·152	·134	·125	·134	35	,, ,,
34	·112	·150	·125	·118	·112	34	Hepatomegaly due to
1 week later.	·100	·142	·120	·100	—	42	passive congestion.
35	·106	·100	·112	·094	—	5	Wilson's disease.
36	·086	·118	·098	·086	·090	35	,, ,,

TABLE VI.—*Continued.*

Case No.	Percentage of sugar in the blood.					% Increase in blood sugar.	Disease.
	Fasting.	Hours after lævulose.					
		½	1	1½	2		
Group III							
37	·098	·126	·106	·096	—	28	Acholuric jaundice.
1 year later.	·100	·106	·098	·100	—	6	
38	·100	·125	·131	·136	·131	36	
1 year later.	·086	·100	·098	·081	—	20	,, ,,
39	·075	·094	·075	·081	—	25	Ketosis and gastro-enteritis.
40	·091	·085	·108	·094	—	19	,, ,,
41	·112	·126	·124	·106	—	8	,, ,,
42	·084	·098	·093	·084	—	16	,, ,,
43	·100	·106	·100	·098	—	6	Cœliac disease.
44	·098	·106	·100	·100	—	8	,, ,,
45	·087	·085	·094	·080	—	8	,, ,,

Discussion.

A review of all the results of the lævulose test detailed above reveals the fact that so far as the normal child is concerned there was not observed in a single instance a delayed fall in the return to the fasting level of the blood sugar. The level of the blood-sugar curve after the ingestion of lævulose showed, however, as pointed out by Tallerman[14], the greatest variations between a definite fall of 10 per cent. and a rise of 28 per cent. It is suggested that the above range should be taken as representing the normal, a conclusion which gains support from the behaviour of the blood-sugar curve in the examples of definite, probable, and problematical hepatic disease which were examined.

Whether or not one would expect an abnormal behaviour of the blood-sugar curve after the administration of lævulose depends on the manner in which this substance is metabolized. If, as previously suggested, the different behaviour of glucose from lævulose depends on whether or not the liver cells are able to convert lævulose into glucose, then naturally the result of the test will depend on the integrity of the liver cells.

It will no doubt be conceded that the functional activity of the liver varies not only in different cases on account of differences in the size of the organ, but also from time to time in the same individual, because of a varying activity of the cells of which the organ is composed. These factors probably account for the variations observed in different normal individuals.

We know, too, that the functional activity of all organs in health is in excess of their physiological requirements. This is specially true of organs which have the power of undergoing hypertrophy, as, for example, the heart and the kidneys; both of these can be the seat of a moderate amount of disease and yet adequately cope with the physiological needs and thus apparently function normally. Consequently it would not seem surprising that the liver might be the seat of a disease which has destroyed only a certain quota of the liver cells or interfered to a certain extent with the activity of

all the cells, and yet not disclose any deficiency of its powers. In this connection one might contrast multilobular cirrhosis, where extensive bands of fibrous tissue interfere with and replace the true liver tissue, with jaundice from an obstruction of the main ducts, where the bile is dammed throughout the whole organ. In the latter condition any change in the hepatic cells will be generalized, and, as a matter of fact, we find that it is here, where the functional activity of the liver is apparently more widely impaired, that the most marked positive lævulose test is obtained.

It is possible, too—in fact, certain—that other organs in some way influence the activity of the liver, and also that the rate of absorption from the gastro-intestinal tract will play a part, so that extra-hepatic disease may be the cause of an apparent hepatic inefficiency.

In view of all these considerations one must be prepared for great variations in the results of such a functional test, not only in health but also in hepatic disease. Consequently the degree of consistency obtained is remarkable when the patients investigated are grouped, according to whether there is definite, probable, or problematical disease of the liver.

In the cases where from the clinical or post-mortem examination definite evidence of disease of the liver was found, it will be noted that 76 per cent. gave what we consider a definitely pathological increase in the blood sugar, and 79 per cent. of these showed a prolongation of the curve. In no case was a delay in the return to the fasting blood-sugar level noted without at the same time an abnormally increased blood sugar.

In the second group of cases where disease of the liver was probable 55 per cent. gave a definitely abnormal rise and 33 per cent. of these gave also a prolonged fall. One case of possible Hanot's disease which was negative became positive 9 months later, although clinically the condition remained the same.

A certain number of diseased conditions were examined, which presented clinically no evidence of disease of the liver but where from the nature of the illness some impairment of hepatic function might exist. Only one, a case of acholuric jaundice (No. 38) showed a definite abnormal rise, but this patient, examined one year later after splenectomy, gave a normal curve.

Conclusions.

1. The hæmoclastic crisis test performed in 20 normal and 25 abnormal conditions of childhood was found to give inconsistent results.

2. In the normal individual variations in the sugar content of the blood after the ingestion of lævulose range from a fall of 10 mgrm. to a rise of 28 mgrm.

3. These variations could not be accounted for by the age of the child.

4. A rise of more than 30 per cent. in the blood-sugar content after the administration of lævulose is considered evidence of hepatic disease.

5. The purity of the lævulose is a most important element in the test.

6. The lævulose test was positive in the majority of examples of definite hepatic disease.

7. The lævulose test gave no evidence that the liver is affected in ketosis or cœliac disease.

8. In some cases in which the clinical evidence leaves a doubt as to the diagnosis the lævulose test may be of value, a positive curve, i.e., an increase in the blood sugar of more than 30 per cent. with or without a prolonged curve, indicating definite and probably extensive derangement of the function of the liver.

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THE NORMAL CEREBRO-SPINAL FLUID IN CHILDREN.

BY

DONALD STEWART, M.D.

(From the Royal Hospital for Sick Children, and the Laboratory of the Royal College of Physicians, Edinburgh.)

For comparison with the findings in disease, it is necessary to determine the characteristics of the cerebro-spinal fluid in healthy infants and children. Comparatively little work has been done on this subject. In the latest work on the cerebro-spinal fluid, *The Human Cerebro-spinal Fluid*, published by the Association for Research in Nervous and Mental Diseases, New York, McLean and McIntosh[1] introduce their chapter on the cerebro-spinal fluid in infants and young children, with a brief account of the normal fluid. They do not state the number of cases examined, but their conclusions are no doubt based on observations sufficiently wide to ensure a reasonable degree of accuracy. Wilcox and Lyttle[2], in a paper on the chemical composition of the spinal fluid in childhood, give their results in a series of twenty-three normal cases.

In the present investigation, fifty cases were examined, a number probably large enough to enable us to form an accurate conception of the condition of the fluid in health. As will be seen from Table I, the children have been divided into eight age groups; the youngest child examined was seven days old, and the oldest twelve years. It will be seen also, that twenty-eight of the fifty cases were children under two years of age.

TABLE I.

AGE GROUPS OF FIFTY CHILDREN EXAMINED.

Age group.	Age limits.				No. of cases.
1	7 days	to	3 months		10
2	3 months	to	1 year		10
3	1 year	to	2 years		8
4	2 years	to	3	,,	5
5	3 ,,	to	5	,,	5
6	5 ,,	to	7	,,	4
7	7 ,,	to	10	,,	4
8	10 ,,	to	12	,,	4

The children whose cerebro-spinal fluid was withdrawn for this study were all in a healthy condition. Each was examined carefully before the punctures were performed.

A comparative study of the normal fluid obtained from different sites was also undertaken. In each of the fifty cases the lumbar fluid was examined; in thirty-five the cistern fluid, and in nine the ventricular fluid was examined.

The work described in this paper does not claim to represent a complete investigation of the normal cerebro-spinal fluid in children. It is rather a study of the commoner aspects of the subject. But it is just those commoner aspects that are of special importance to the clinician, and it is hoped accordingly that the results here shown may serve a useful purpose from the view-point of clinical diagnosis.

The following are the points included within the investigation :—1. Pressure studies. 2. Cytology. 3. Protein Content. 4. Sugar Content. 5. Chloride Content.

1. Pressure Studies.

The fluid pressure was estimated manometrically in ten children. A simple aneroid manometer, such as described by Levinson[3], was used for these observations. The measurements were taken at lumbar puncture, immediately after the insertion of the needle, with the child in the sitting position. Table II gives the results in these cases.

TABLE II.

PRESSURE OF CEREBRO-SPINAL FLUID AT LUMBAR PUNCTURE.

	Age.	Pressure.	Observations.
1	10 weeks	35 mm.	Cried hard all the time.
2	3 months	75 ,,	Absolutely still.
3	9 ,,	240 ,,	Spasmodic crying ; pressure rose and fell 110 mm., with crying fits.
4	10 ,,	110 ,,	Very restless ; struggled hard. Reading varied 60—100 mm.
5	4 years	94 ,,	Respirations 30—40 at times ; otherwise nil to note.
6	6½ ,,	300 ,,	Continual movement, although held by two assistants. Variation of 30—100 mm.
7	10 ,,	50 ,,	Absolutely still. No variation in reading.
8	11 ,,	160 ,,	Absolutely still. No variation in reading.
9	11 ,,	200 ,,	Slight cough ; reading varied 30—50 mm.
10	11 ,,	190 ,,	Struggled hard ; cried and coughed. Reading varied 50—60 mm. even with slight movement ; 100—120 with crying and coughing.

From the differences disclosed in these readings (Table II), it becomes apparent that in normal children it is difficult to obtain accurate manometric results. There are many factors by which the pressure is influenced. The position of the patient, to begin with, is a matter of importance. Ayer[4] states that " in the sitting position the lumbar pressure is approximately doubled, while at the cisterna magna the pressure is below zero, *i.e.*, a negative pressure ; similarly the ventricular pressure is negative, a fact which can be readily checked by palpation of the normal infant's fontanelle." Infants and young children commonly resent lumbar puncture. They sometimes cry, cough, sneeze, hold their breaths, or even struggle and move their bodies. All these factors materially affect the pressure, any one of them being sufficient to send it up 100 mm. or more. It may therefore be concluded that in infants and in young children manometric estimation of the fluid pressure is unreliable, and accordingly of no diagnostic value to the pædiatrician.

TABLE III.

CELL-COUNTS IN DIFFERENT AGE GROUPS.

Age group.	Case No.	Age.	Total cells per cubic mm.		
			Lumbar.	Cistern.	Ventricle.
I	1	7 days	34	27	—
	2	15 ,,	28	—	—
	3	27 ,,	18	12	0
	4	5 weeks	20	—	—
	5	7 ,,	24	22	1
	6	8 ,,	18	—	—
	7	10 ,,	16	18	0
	8	11 ,,	23	28	0
	9	3 months	19	15	2
	10	3 ,,	27	—	—
II	11	4 months	18	16	—
	12	4 ,,	10	14	0
	13	6 ,,	15	14	0
	14	6 ,,	9	—	—
	15	7 ,,	21	20	0
	16	9 ,,	8	6	0
	17	9 ,,	17	—	—
	18	10 ,,	15	12	—
	19	12 ,,	24	20	—
	20	12 ,,	11	—	—
III	21	13 months	14	12	—
	22	15 ,,	12	10	—
	23	15 ,,	8	6	—
	24	19 ,,	17	—	—
	25	19 ,,	16	14	—
	26	21 ,,	20	14	—
	27	2 years	15	—	—
	28	2 ,,	10	11	—
IV	29	$2\frac{2}{12}$ years	9	8	—
	30	$2\frac{7}{12}$,,	15	8	—
	31	$3\frac{9}{12}$,,	12	12	—
	32	3 ,,	8	—	—
	33	3 ,,	20	14	—
V	34	$3\frac{1}{2}$ years	15	10	—
	35	$3\frac{8}{12}$,,	17	10	—
	36	4 ,,	14	—	—
	37	5 ,,	10	8	—
	38	5 ,,	4	3	—
VI	39	$5\frac{1}{2}$ years	11	—	—
	40	6 ,,	8	7	—
	41	7 ,,	12	11	—
	42	7 ,,	9	9	—
VII	43	8 years	8	5	—
	44	8 ,,	6	6	—
	45	8 ,,	10	—	—
	46	10 ,,	5	—	—
VIII	47	11 years	8	6	—
	49	$11\frac{1}{2}$,,	4	6	—
	48	12 ,,	3	3	—
	50	12 ,,	7	—	—

Even approximate estimation of the pressure is a matter of great difficulty in children. If the manometer can give results which are almost impossible to interpret, practically nothing can be estimated from the rate of flow of fluid through the needle. In a child, normal in every way, the fluid may spurt out two or three feet at lumbar puncture; while again, in cases of tuberculous meningitis, with definite signs of increased intracranial pressure, and with no block in the spinal-subarachnoid space, the fluid in many cases may not spurt out half as far. The use of the phrase, "the fluid was under pressure," which is based entirely on the rate of flow through the needle, is therefore no indication of the fluid tension, and is apt in many cases to be misleading. Estimation of the pressure by counting the drops per unit of time cannot be too severely condemned. Ayer[4] found that often where fluid came slowly from the needle, the manometric reading rose to pathological heights.

In order to obtain an approximate estimate of the pressure in the fluid of children, various rules have to be observed. Lumbar puncture should be done in all cases with the patient in the same position, and there must be complete elimination, as far as possible, of the disturbing factors already mentioned. How far this is possible may only be ascertained after long experience. In our experience in infants and young children, it is, to all intents and purposes, impossible.

2. Cytology.

In estimating the cell count, a Fuchs-Rosenthal[5] counting-chamber was employed. When red and white blood cells were present, and even when an estimate was approximately arrived at, the cell count was not accurate. Efforts were made in every case to see that there was no blood contamination in the fluids examined.

Table III shows the total cell count in the various age groups.

In Table IV, the lumbar and cistern fluids are compared in the different age groups, as regards (1) the limits of variation in the number of cells per cubic millimetre, and (2) the average number of cells per cubic millimetre.

TABLE IV.

COMPARISON OF CYTOLOGY OF LUMBAR AND CISTERN FLUIDS.

Age group.	Lumbar fluid.		Cistern fluid.	
	Variation.	Average.	Variation.	Average.
1	16—34	23	12—27	20
2	8—24	15	6—20	14
3	8—20	14	6—14	11
4	8—20	12	8—14	10
5	4—17	12	3—15	10
6	8—12	10	6—11	8
7	5—10	7	5—16	6
8	3— 8	6	2— 6	4

The ventricular fluid was examined in nine children, aged twenty-seven days to nine months. One case showed two small lymphocytes, another showed one. The other ventricular fluids contained no cells.

Differential Cell Count.—Small lymphocytes constituted the greater part of every cell count, being from 94 to 100 per cent. of the total count. Frequently large lymphocytes were found, but they did not in any case constitute more than 6 per cent. In no case were polymorphonuclear cells present.

Summary.—1. The total cell count varied in the lumbar fluid from 34 cells per c. mm. in an infant of seven days, to 3 per c.mm. in a child of twelve years ; and in the cistern fluid from 28 per c.mm. in a child of eleven weeks, to 3 per c.mm. in two cases aged five and twelve years respectively.

2. In five cases the cell count in the cistern fluid was greater, in three equal to, and in the remaining twenty-seven less than, the count in the lumbar fluid. The difference was never more than seven, and in the great majority of cases was from one to four.

3. The ventricular fluid in two cases showed 1 and 2 cells per c.mm. respectively. The other fluids, seven in number, contained no cells.

4. The differential count showed that all the cells were mononuclear. Small lymphocytes varied from 94 to 100 per cent., and large lymphocytes up to 6 per cent. of the total count.

Conclusions.—1. The cell count varies approximately with the age of the child, the highest counts being found in the youngest children.

2. In the great majority of cases the cell count is slightly greater in the lumbar fluid than in the cistern fluid.

3. The normal ventricular fluid in infants contains no cells as a rule, but occasionally one or two may be present.

4. In children all the cells are mononuclear, small and large lymphocytes being in the proportion of about 20 : 1.

3. Protein Content.

The value of careful quantitative estimation of protein is obvious. In many diseases of the nervous system the appearance of abnormal amounts of protein in the spinal fluid is one of the earliest abnormal signs. Thus it is essential to know the normal amounts, and, if possible, the amounts to be expected in different pathological conditions. An accurate method of quantitative estimation is therefore necessary.

Method of Estimation.—During the past number of years many methods of estimating the protein content of the cerebro-spinal fluid have been used.

Picric acid methods, either by the ordinary urine albuminometer or with Aufrecht's albuminometer, are at the best only approximate estimations, and the want of a more accurate method was felt for a long time. For some years the French, who were pioneers in cerebro-spinal pathology, have expressed their protein determinations in figures. They used for the most part the Mestrezat[6] trichloracetic acid method, and more recently that advocated by Ravaut and Boyer[7], in which silver chloride is used as a standard.

In 1920, Denis and Ayer[8] described a method for the quantitative determination of protein in the fluid, and this method has been used by them and other workers in America with satisfactory results. They use protein as a standard, and in the estimation an unknown protein precipitate is compared with a known protein precipitate,

TABLE V.

PROTEIN CONTENT IN CEREBRO-SPINAL FLUID.

Age group.	Case No.	Age.	Total protein (mgrm. per 100 c.cm.).		
			Lumbar.	Cistern.	Ventricle.
I	1	7 days	30	25	—
	2	15 ,,	54	—	—
	3	27 ,,	15	12	5
	4	5 weeks	19	—	—
	5	7 ,,	38	35	10
	6	8 ,,	45	—	—
	7	10 ,,	42	30	12
	8	11 ,,	20	18	5
	9	3 months	27	27	10
	10	3 ,,	25	—	—
II	11	4 months	30	30	—
	12	4 ,,	25	20	5
	13	6 ,,	35	30	17
	14	6 ,,	34	—	—
	15	7 ,,	39	35	18
	16	9 ,,	45	40	12
	17	9 ,,	55	—	—
	18	10 ,,	38	30	—
	19	1 year	50	40	—
	20	1 ,,	42	—	—
III	21	13 months	37	30	—
	22	15 ,,	30	25	—
	23	15 ,,	42	40	—
	24	18 ,,	45	—	—
	25	19 ,,	50	38	—
	26	21 ,,	17	17	—
	27	2 years	24	—	—
	28	2 ,,	35	30	—
IV	29	$2\frac{2}{12}$ years	20	17	—
	30	$2\frac{7}{12}$,,	23	23	—
	31	$2\frac{9}{12}$,,	28	20	—
	32	3 ,,	34	—	—
	33	3 ,,	35	35	—
V	34	$3\frac{1}{2}$ years	45	40	—
	35	$3\frac{8}{12}$,,	34	30	—
	35	4 ,,	19	—	—
	37	5 ,,	50	50	—
	38	5 ,,	42	35	—
VI	39	$5\frac{1}{2}$ years	38	—	—
	40	6 ,,	50	27	—
	41	7 ,,	27	18	—
	42	7 ,,	28	20	—
VII	43	8 years	32	30	—
	44	8 ,,	25	15	—
	45	8 ,,	15	—	—
	46	10 ,,	36	—	—
VIII	47	11 years	45	30	—
	48	$11\frac{1}{2}$,,	20	15	—
	49	12 ,,	27	18	—
	50	12 ,,	35	—	—

The method of Denis and Ayer has two important advantages over the other methods in use, namely, the small amount of fluid necessary for the test, and the short time taken to complete the test. Usually a number of examinations have to be undertaken on a small amount of fluid, and so the advantages of a test which necessitates the use of only 0·6 c.cm., or at most 1 c.cm., are obvious. The protein content may be estimated in one fluid in about ten minutes, and twenty fluids can be examined in less than half an hour.

In the present series of tests the protein was determined by the method of Denis and Ayer on the first 3 c.cm. of fluid, assuming that the amount of fluid withdrawn might modify the protein content.

Table V shows the readings from lumbar, cistern and ventricular fluids, in the various age groups in mgrm. per 100 cc.

It will be seen from the above table that there is no variation of the total protein with the age of the patient, such as was noted in the cell count.

From Table VI it may be seen that the readings in the lumbar fluid vary from 15 to 55 mgrm. per 100 c.cm., with an average of 33 mgrm. In the cistern fluid, the variation was from 12 to 50, the average being 28 mgrm. In nine ventricular fluids, the readings varied from 5 to 18, with an average of 11 mgrm. per 100 c.cm.

TABLE VI.

AVERAGE IN PROTEIN CONTENT.

	Total protein (mgrm. per 100 c.cm.).		
	Lumbar.	Cistern.	Ventricle.
Limits of variation ...	15—55	12—50	5—18
Average	33	28	11

Ayer and Foster[9], using the method of Denis and Ayer, found that the amount of protein normally present in the lumbar fluid in patients of all ages, varies between 15 and 45 mgrm. per 100 c.cm. Mestrezat[6] considers 15 to 30 mgrm. as normal, and the error in his diaphanometric method is stated by Greenfield and Carmichael[10] to be less than 20 per cent. Eskuchen[11] gives 20 to 30 mgrm. as normal. Young and Bennett[12], using a method of their own with 95 per cent. ethyl alcohol as the precipitating agent, find that normal fluids contain 25 to 75 mgrm. per 100 c.cm.

Fremont-Smith and Ayer[13] state that in the cisterna magna the normal range is from 10 to 25 mgrm., and in the ventricles from 5 mgrm. or less, to 15 mgrm. In one case of a child aged five years, normal in every respect, the present writer found 50 mgrm. in the cistern fluid: but his highest reading in the ventricular fluid was 18 mgrm. per 100 c.cm.

It is interesting to note that, in the main, our results resemble those of Ayer and Foster[9], who originally used this method. In children, we have found higher figures in cistern fluids than they did in patients of all ages, and in many cases not so much difference between the lumbar and cisternal content.

Summary. The total protein in the lumbar region varied from 15 to 55 mgrm. per 100 c.cm., with an average of 33; in the cisterna magna from 12 to 50, average 28; and in the ventricle from 5 to 18, giving an average of 11 mgrm. per 100 c.cm.

Conclusions. 1. The protein content in the lumbar fluid does not vary with the age of the child.

2. The protein content in the lumbar fluid of children is similar to that in the lumbar fluid of adults.

3. In children there is less difference than in adults between the total protein in the lumbar and cistern fluids.

4. The protein content in the ventricular fluid of infants is similar to that in the ventricular fluid of adults.

4. Sugar Content.

The sugar content of the normal cerebro-spinal fluid was estimated in thirty cases. In each case the blood sugar was also estimated, Maclean's[14] method being used for both.

Relation of the spinal fluid sugar to the blood sugar. The relation between the spinal fluid sugar and the blood sugar has long been a subject of controversy, but most workers now agree that, normally, the sugar content of the

TABLE VII.

COMPARISON OF SUGAR IN CEREBRO-SPINAL FLUID AND BLOOD.

No.	Age.	Fluid sugar (mgrm. per 100 c.cm.)	Blood sugar (mgrm. per 100 c.cm.)	%
1	7 days	70	138	50
2	15 ,,	49	91	54
3	27 ,,	55	79	70
4	7 weeks	42	83	50
5	10 ,,	57	85	60
6	11 ,,	44	84	52
7	3 months	76	110	49
8	4 ,,	58	90	64
9	4 ,,	82	147	55
10	6 ,,	39	67	58
11	7 ,,	48	72	66
12	9 ,,	42	74	55
13	12 ,,	53	75	66
14	13 ,,	74	120	62
15	15 ,,	59	87	61
16	21 ,,	84	150	55
17	2 years	71	146	50
18	$2\frac{7}{12}$,,	58	70	82
19	$2\frac{3}{4}$,,	62	98	63
20	3 ,,	28	67	42
21	4 ,,	51	104	50
22	5 ,,	47	90	52
23	6 ,,	49	85	58
24	7 ,,	57	88	63
25	8 ,,	73	121	60
26	8 ,,	27	56	48
27	10 ,,	67	93	72
28	11 ,,	55	114	47
29	12 ,,	54	109	50
30	12 ,,	58	118	49

spinal fluid is from 40 to 60 per cent. of the sugar content of the blood. By itself the fluid-sugar estimation is not of much value, but when expressed as a percentage of the blood sugar, it is of definite use to the clinician. Nawratski[15], Ino[16], and Kimura[17] have all shown that in dogs and rabbits the spinal fluid sugar follows the blood-sugar changes after a latent period, and Goodwin and Shelley[18] have concluded from their work on the subject that the percentage relation between the two is fairly constant at from 45 to 65 per cent.

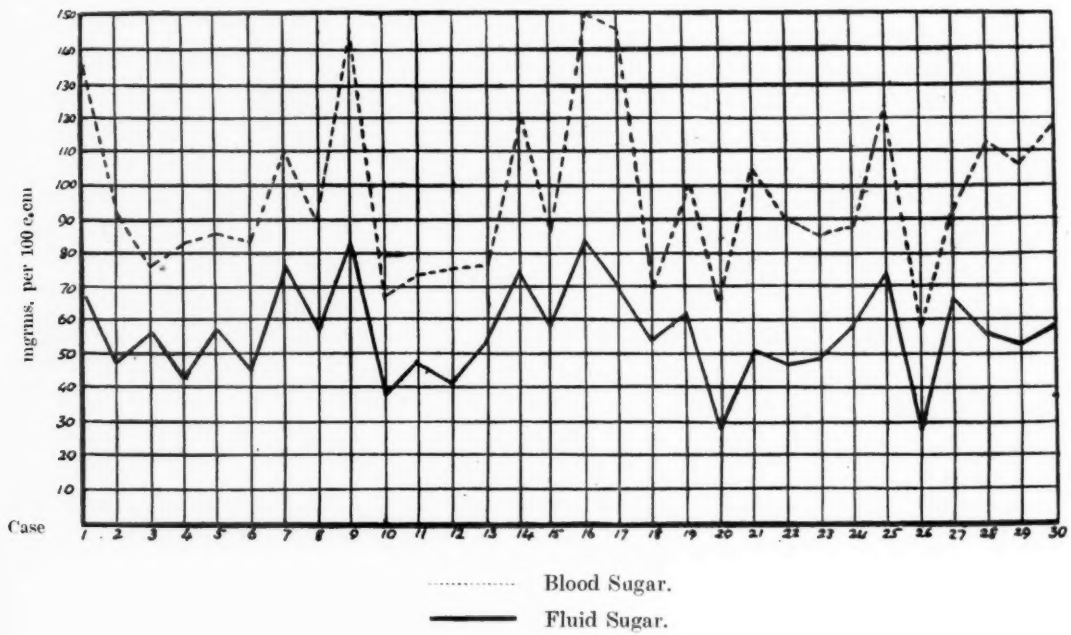
Table VII shows the sugar content in thirty lumbar fluids of normal infants and children. The fluids were withdrawn, as far as possible, from 'fasting' children. The blood sugar was also estimated in every case. In the last column, the fluid sugar is expressed as a percentage of the blood sugar.

From this table it may be seen that the spinal fluid sugar varied from 42 to 82 per cent. of the blood sugar. In one case it was 82 per cent., in one 72, and another 70 per cent. The great majority of the cases lay between 45 and 66 per cent. of the blood sugar. It may also be seen that in no case was the fluid sugar more than the blood sugar.

The amount of sugar in the lumbar fluid varied from 27 to 84 mgrms. per 100 c.cm., the majority of the readings being between 45 and 70 mgrm.

The blood sugar varied from 56 to 140 mgrm. per 100 c.cm.

GRAPH SHOWING RELATIONSHIP OF FLUID AND BLOOD SUGAR.



The sugar content of the cistern fluid was estimated in ten of the cases. In every case the readings were almost identical with those from the lumbar fluid. These are shown in Table VIII, compared with the blood-sugar readings.

TABLE VIII.

COMPARISON OF SUGAR IN CISTERN FLUID AND BLOOD.

Case No.	Age.	Fluid sugar (mgrm. per 100 c.cm.).		Blood sugar (mgrm. per 100c. cm.)
		Cistern.	Lumbar.	
3	27 days	57	55	79
4	7 weeks	41	42	83
5	10 ,,	55	57	85
10	6 months	40	39	67
11	7 ,,	49	48	72
12	9 ,,	43	42	74
15	15 ,,	60	59	87
17	2 years	73	71	146
19	$2\frac{3}{4}$,,	62	62	98
22	5 ,,	49	47	90

In nine of the cases the sugar content of the ventricular fluid was estimated. In every case it was higher than the content of the lumbar and cistern fluids, but not so high as the blood sugar. This agrees with the observations of Cestan, Riser, and Laborde[19]; and Fremont-Smith and Dailey[20] in a small series of cases obtained similar results. Table IX shows the readings compared with the lumbar and cistern content, and with the blood sugar.

TABLE IX.

COMPARISON OF SUGAR IN VENTRICULAR FLUID AND BLOOD.

Case No.	Age.	Fluid sugar (mgrm. per 100 c.cm.).			Blood sugar (mgrm. per 100 c.cm.).
		Ventricle.	Cistern.	Lumbar.	
3	27 days	64	57	55	79
4	7 weeks	44	41	42	83
5	10 ,,	59	55	57	85
6	11 ,,	53	—	44	84
7	3 months	80	—	76	110
9	4 ,,	97	—	82	147
10	6 ,,	45	40	39	67
11	7 ,,	53	49	48	72
12	9 ,,	59	43	42	74

Summary. 1. The lumbar fluid sugar varied from 42 to 82 per cent. of the blood sugar. The great majority of the cases lay between 45 and 66 per cent. of the blood sugar.

2. The amount of sugar in the lumbar fluid varied from 27 to 84 mgrm. per 100 c.cm.

3. The sugar content of the cistern fluid was practically identical with that of the lumbar fluid in the ten cases investigated, eight cases showing an increase of only from 1 to 2 mgrm., the other two cases being equal and 1 mgrm. less respectively.

4. In the nine cases examined the sugar content of the ventricular fluid was higher than in the lumbar and cistern fluids, but not so high as in the blood.

Conclusions. 1. The spinal fluid sugar should always be expressed as a percentage of the blood sugar.

2. In normal children the spinal fluid sugar is 45 to 66 per cent. of the blood sugar.

3. In children the sugar content of the cistern fluid normally is 1 to 2 mgrm. higher than that of the lumbar fluid.

4. The sugar content in the ventricular fluid in infants is considerably higher than in either the cistern or lumbar fluid.

5. Chloride Content.

The chloride content of fifty lumbar fluids was estimated. The cistern fluid was examined in thirty-five of these cases, and the ventricular fluid in nine.

Table X shows the readings from these different loci.

Fremont-Smith and Dailey[20] state that the normal chloride of the cerebro-spinal fluid in adults varies between 720 and 750 mgrm. per 100 c.cm. Mestrezat[6] gives 725 to 740 mgrm., and Eskuchen[11] finds that the normal variation lies between 725 and 750 mgrm. per 100 c.cm.

McLean and McIntosh[1] state that in infants and young children, the chloride content varies from 600 to 750 mgrm. per 100 c.cm. of fluid.

Fremont-Smith and Dailey[20] also found that "an individual, fasting and at rest, will have normally the same chloride content in lumbar, cistern, and ventricular fluid," which is in agreement with the results of Cestan, Riser, and Laborde.[19]

Summary. 1. The chloride content of the lumbar fluids examined varied from 636 to 763 mgrm. per 100 c.cm.

2. The chloride content of the cistern and ventricular fluids was practically identical with that of the lumbar fluid.

Conclusions. 1. The chloride content of the cerebro-spinal fluid in children varies from 630 to 760 mgrm. per 100 c.cm., as compared to the more or less constant level of 720 to 750 mgrm. per 100 c.cm. in adults.

2. In normal children, the chloride content is the same in lumbar, cistern, and ventricular fluids.

Summary and Conclusions.

It may be advisable now to summarize briefly the results obtained in the examination of the fluids.

(1) The pressure studies were only of negative value, but were none the less interesting. They proved the uselessness of manometric readings in young children, where so many disturbing features may be present to upset the calculations. They showed, also, the extreme inaccuracy of estimating the fluid tension by observation of the rate of flow.

(2) The cell count was found to be normally from 20 to 30 per c. mm. in infants, and to decrease gradually as the age increases, becoming identical with that of adults (3—7) at the age of 10 to 12 years.

(3) The total protein content, estimated by the method of Denis and Ayer, was found to approximate in amount to the content in adults. In the lumbar region it varied from 15 to 55 mgrm.; in the cisterna magna from 12 to 50 mgrm.: and in the lateral ventricles from 5 to 18 mgrm. per 100 c.cm.

TABLE X.

CHLORIDE CONTENT OF CEREBRO-SPINAL FLUID.

Age group.	Case No.	Age.	Chlorides (mgrm. per 100 c.cm.).		
			Lumbar.	Cistern.	Ventricular.
I	1	7 days	670	667	—
	2	15 ,,	710	—	—
	3	27 ,,	636	640	632
	4	5 weeks	705	—	—
	5	7 ,,	690	688	691
	6	8 ,,	674	—	—
	7	10 ,,	663	667	665
	8	11 ,,	708	713	705
	9	3 months	689	685	694
	10	3 ,,	716	—	—
II	11	4 months	723	730	—
	12	4 ,,	706	711	705
	13	6 ,,	659	653	657
	14	6 ,,	742	—	—
	15	7 ,,	679	675	668
	16	9 ,,	703	709	711
	17	9 ,,	732	—	—
	18	10 ,,	695	690	—
	19	12 ,,	731	738	—
	20	12 ,,	727	—	—
III	21	13 months	720	721	—
	22	15 ,,	687	679	—
	23	15 ,,	694	690	—
	24	18 ,,	703	—	—
	25	19 ,,	715	719	—
	26	21 ,,	693	705	—
	27	2 years	718	—	—
	28	2 ,,	688	696	—
IV	29	$2\frac{0}{12}$ years	735	740	—
	30	$2\frac{7}{12}$,,	709	715	—
	31	$2\frac{9}{12}$,,	697	705	—
	32	3 ,,	730	—	—
	33	3 ,,	712	712	—
V	34	$3\frac{1}{2}$ years	734	736	—
	35	$3\frac{8}{12}$,,	699	710	—
	36	4 years	725	—	—
	37	5 ,,	692	697	—
	38	5 ,,	718	710	—
VI	39	$5\frac{1}{2}$ years	726	—	—
	40	6 ,,	735	735	—
	41	7 ,,	718	704	—
	42	7 ,,	763	759	—
VII	43	8 years	717	719	—
	44	8 ,,	739	730	—
	45	8 ,,	713	—	—
	46	10 ,,	683	—	—
VIII	47	11 years	729	723	—
	48	$11\frac{1}{2}$,,	740	748	—
	49	12 ,,	713	728	—
	50	12 ,,	728	—	—

(4) The sugar content of the fluid in children varies directly with the blood-sugar. In order to be of most use to the clinician therefore, estimation of the fluid sugar should be accompanied by the estimation of the blood sugar. It was found that this relation of the spinal fluid sugar to the blood sugar in children is similar to that which exists in adults.

(5) The chloride content in children was found to vary normally from 630 to 760 mgrm. per 100 c.cm., that is a variation of 130 mgrm. The adult fluid has a fairly constant chloride content of from 720 to 750 mgrm. per 100 c.cm., that is a variation of only 30 mgrm.

The chemical and cytological examinations of the fluids were carried out from the Royal College of Physicians' Laboratory, Edinburgh, and to the Curator, Sir Robert Philip, and to the Committee of the Laboratory, I am indebted for permission to work there. To Dr. Charles McNeil, Dr. N. S. Carmichael, and Dr. Lewis Thatcher my thanks are due for permission to use their cases in the Royal Hospital for Sick Children, Edinburgh. To the late Dr. J. W. Dawson, and to Dr. Fergus Hewat and Mr. N. M. Dott, I have also to acknowledge my indebtedness for valuable assistance in many ways.

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TRANSPLANTATION OF URETERS FOR CONGENITAL INCONTINENCE : A FINAL RESULT.

BY

GEORGE A. MASON, M.B., B.S.

Surgical Registrar, Royal Victoria Infirmary, Newcastle-upon-Tyne,
Assistant Curator, Pathological Museum, University of Durham
College of Medicine.

Recent communications (Foulds and Robertson[1], Starr[2]) on late results after transplantation of the ureters into the rectum for the alleviation of urinary incontinence of congenital origin appear to be sufficient justification for the publication of the clinical record of an allied type of case, together with an account of the state of affairs found post mortem.

The patient was operated upon by Professor Grey Turner at the Royal Victoria Infirmary, Newcastle-upon-Tyne. Death occurred from an independent condition three years later, and I am indebted to Professor Turner for his permission to dissect the specimen and to publish this record.

Clinical Record.

J. F., a boy, aged 10½ years, was admitted to the hospital on March 19th, 1922. He had suffered from incontinence of urine, with all its disagreeable consequences, since birth. His education had been very seriously retarded, and his life was a misery. Apart from an attack of scarlatina some few months before admission, and measles at the age of four years, there was nothing of importance in the past history. He was, however, said to have never been very strong.

On examination, the general health appeared to be fairly good. Locally there was a condition of complete epispadias, and the resulting incontinence had caused excoriation of the skin over the lower abdomen and scrotum. The child's general health, and the fact that he had successfully weathered the storms of the acute exanthemata, were taken into consideration, and the choice of operation lay between a local plastic operation and transplantation of the ureters into the rectum. Professor Turner having had greater experience of the success attendant upon the latter procedure decided to employ it in this case.

Operation No. 1.—25.3.22. General anæsthesia. Mid-line incision. The left ureter was approached by the transperitoneal route, mobilized and after division low in the pelvis was transplanted into the sigmoid colon after the oblique manner recommended by Stiles[3]. A small rubber drainage tube was placed down to the region of the anastomosis; in addition, a short tube was passed through the anus into the rectum to prevent distension of that organ.

The child stood the operation very well. It was followed by a fairly vigorous renal reaction as evidenced by the temperature, which reached its highest point 100·8° F. on April 4th, and tenderness over the left kidney.

Operation No. 2.—22.4.22. General anæsthesia was again employed and the old incision re-opened. The right ureter was implanted by a similar procedure into the sigmoid as was the left at the previous operation; similar drainage being employed as before. In addition it was

observed that :—(*a*) The previous anastomosis was well protected by the parietal peritoneum having been sutured over it ; (*b*) the left ureter could be felt in the bowel wall (as a thickening) reminiscent of rectal polypus ; (*c*) the rectum appeared to be more distended and hypertrophied than at the previous operation ; (*d*) on opening the bowel after the application of the clamp, clean urine escaped ; this suggested that it would have been advisable to have passed a rectal tube before commencing the operation.

A good recovery was made from this operation also, but a definite attack of renal infection again occurred with some night fever up to 100·4° F. which continued until May 1st.

By May 9th twenty-five ounces of urine were being passed from the rectum per diem. This urine had a specific gravity of 1010, a thick, dirty, yellow appearance, a ropy deposit, an ammoniacal smell and an alkaline reaction.

On May 11th, the entry in the hospital notes reads thus :—" The patient is bright and happy. He passes his urine per rectum with perfect ease and continence about four times a day, and his bowels move comfortably about three times a day. The motion is a fluid one. His temperature and pulse are normal. He sleeps and eats well, and states that he feels better than ever he has done before in all his life. His abdominal wound is healed perfectly and there is no sign of skin irritation left over the lower abdomen and scrotum. The patient is now pleased with life and looks forward to the future with renewed hope and vigour." On May 16th, 1922, he was discharged from hospital.

After History.—The boy remained perfectly well until May, 1925, 3 years later, when he was admitted under the care of another clinic with a history that during the previous twenty-four hours he had been having recurring attacks of colic. The child appeared to be in very good condition, and nothing abnormal was discovered on physical examination. The possibility of the attacks being renal in origin was at first considered, but after two days of fruitless observation he was sent home. A few days later, however, he was re-admitted to hospital looking very ill, and on developing, some hours afterwards, copious fæculent vomiting, a laparotomy was performed.

There was found an acute obstruction of the small intestine due to a band in association with tuberculous mesenteric glands. A lateral anastomosis was performed. At the end of the operation there was a marked degree of collapse, but this was speedily overcome and for a while all appeared to be going well. Unfortunately, after two days, a change for the worse was manifest and the condition rapidly retrogressed, death occurring on the fifth day.

Post-Mortem Examination.

On the day after death a necropsy was made. The lower bowel and urogenital organs were removed for preservation preparatory to further dissection (*vide infra*). In the peritoneal sac there was a suppurative peritonitis binding the coils of intestine together. Some of the sutures at the anastomosis had given way and fæcal matter had escaped. The mesenteric glands were distinctly enlarged and caseous, some being definitely calcareous. These had apparently given rise to fibrous bands which had caused the intestinal obstruction.

From the preserved mass, referred to above, the kidneys, ureters and lower bowel were dissected. Fig. 1 is from Mr. Sewell's drawing of the specimen thus obtained.

The rectum appears to be distended and its muscle definitely hypertrophied. The mucosa below the level of the ureteric orifices is coated with a shaggy inflammatory exudate ; microscopically this region is the seat of a mild catarrhal inflammation, whilst above this level the mucosa is smooth and appears healthy both on naked-eye and microscopic examination. This slight degree of catarrhal inflammation could probably be explained by the irritation consequent on ammoniacal decomposition of the urine.

The right ureteric orifice is patulous ; its mucosa has prolapsed, giving it a button-like appearance, and it is the seat of inflammatory change similar to that seen in the neighbouring rectal mucosa.

The left ureteric orifice was very difficult to find and is represented by a mere slit through which a fine bristle has been passed, contrasting with its fellow which has admitted with ease a glass rod of much greater magnitude. So difficult was the orifice to find that it had to be demonstrated by squirting fluid into the ureter above and searching for the issuing stream.

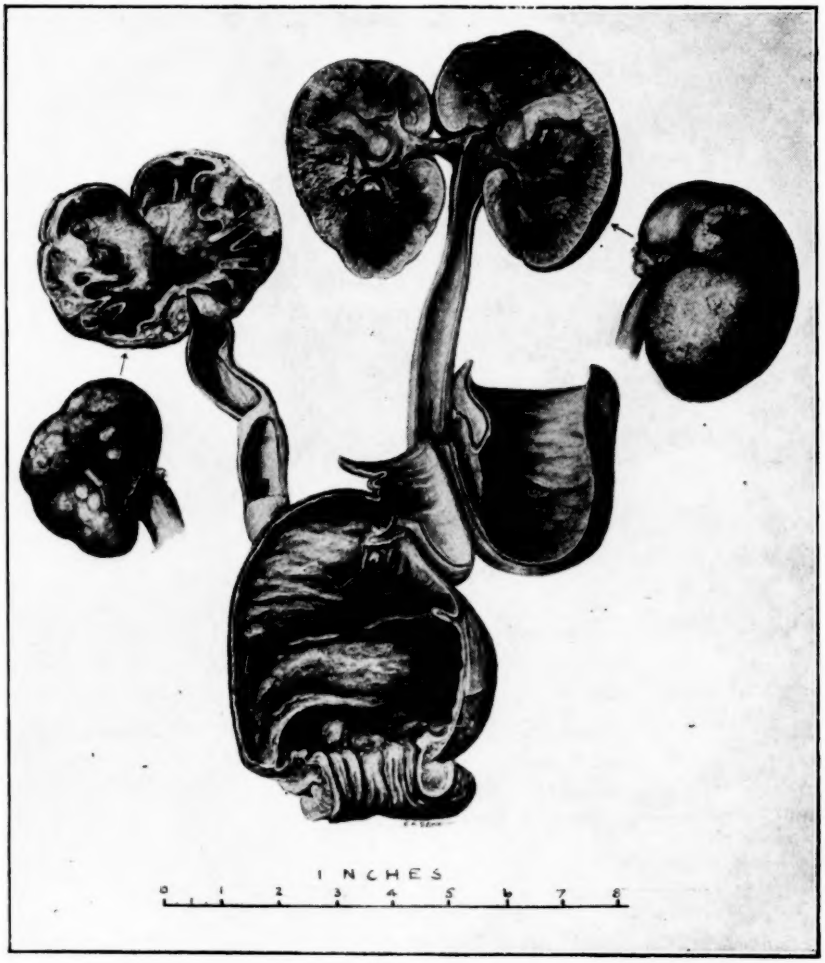

Fig. 1. Dissection of specimen illustrating condition of organs three years after transplantation of ureters into the rectum.

The right kidney is markedly shrunken. Its surface is scarred. On section the organ consists mainly of the dilated pelvis and calyces. The condition is an advanced pyonephrosis. Microscopic examination of such renal tissue as remains shows extensive fibrosis, hyaline changes and round cell infiltration in the glomerular region. The tubules show cloudy swelling. Areas of necrosis with accumulation of polymorphonuclear leucocytes are also present, and in these there are a few bacteria.

The left kidney is of normal size. Its surface is also somewhat scarred. In the section some of the pyramids are much darker than the cortex. The cortex is swollen and the vascular markings stand out prominently. The pelvis and calyces are slightly distended, the former merging imperceptibly with the ureter. Histologically the cortex (Fig. 2) shows areas in which some of the glomeruli are fibrosed, others show slight lobulation, and in addition there is a round-cell infiltration. The tubules show little change apart from cloudy swelling. The areas of fibrosis represent healing after a previous acute nephritis, probably a " flare up " after a transplantation operation. The lobulated glomeruli, etc., indicate the presence of a subacute inflammation of the kidney, probably, in view of the distended ureter, of the nature of an ascending pyelonephritis. A considerable number of fields exhibited relatively normal renal tissue. It is possible that the areas of necrosis containing bacilli, etc., seen in the right kidney represent a terminal pyæmic process from the septic peritonitis.

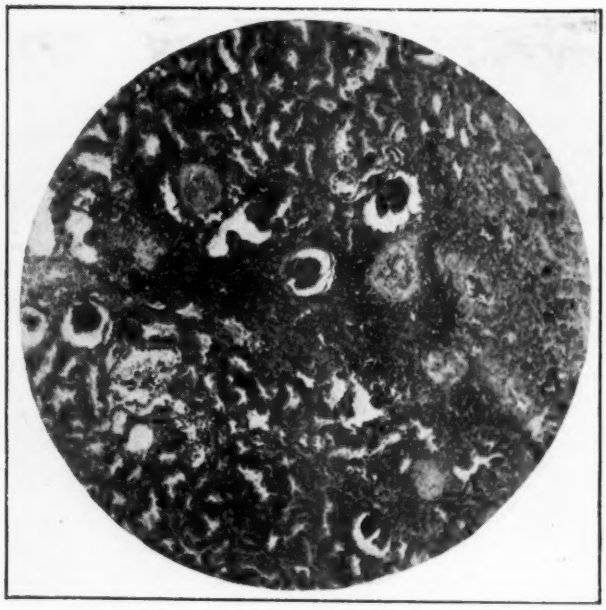

Fig. 2. Section of Left Kidney (× 60)

The ureters when opened contained a quantity of purulent fluid. Both ureters are dilated but the wall of the right is the thicker. The right ureter is also shorter, more tortuous and about its middle there is a definite annular narrowing.

Histologically there is evidence of the ureteric infection (Fig. 3).

Fig. 3. Section Right Ureter (× 60).

Conclusions.

After transplantation of the ureters a life may be lived which is to all intents and purposes normal. The rectum being able to tolerate the presence of urine in its lumen, control is soon established, and voluntary evacuations are obtained at convenient intervals.

Despite the apparently advanced degree of renal infection found post mortem, this child, until a few days before the end, not only appeared healthy but actually led the ordinary life of a school child without any inconvenience.

In this, as in other similar cases, there was probably already an established ureteric infection before any operative interference was attempted. Although no mention is made in the clinical record, it is probable that in this case, as is often found, the ureters were somewhat dilated before transplanting. Despite this the reserve of renal efficiency was such as to withstand successfully not only two relatively severe operations, but even to survive the acute exacerbation of the renal infection, which occurred after each operation.

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ANALYSIS OF THE BLOOD GROUPS OF CHILDREN AND INFANTS.

BY

ELSIE V. CROWE, M.B., Ch.B., Edin.

(From the Royal Hospital for Sick Children, Edinburgh).

It has long been known that, if the blood of one species of animal is injected into the circulation of another species, the corpuscles of the foreign blood are at once destroyed and their hæmoglobin set free. An analogous hæmolysis may occur when the bloods of certain individuals are mixed with those of other individuals of the same species, and the observation of this fact led to the discovery of blood groups among human beings.

Landsteiner[1] discovered hæmolysins and iso-hæmolysins twenty-seven years ago. Six years later Jansky[2] divided human blood into four groups, and showed that the blood of each group had a definite relationship to each of the other three groups. In 1910 Moss[3] amplified these discoveries and pointed out that the hæmolysis is always preceded by agglutination, and that the interaction between the groups might stop at agglutination.

There are thus two sets of independent reactions between the serum of the one group and the corpuscles of the other, the serum of the one agglutinating or hæmolysing the corpuscles of the other.

First Reaction. The corpuscles of Group I are agglutinated by the sera of Groups II, III and IV; those of Group II are agglutinated by the sera of Groups III and IV; those of Group III by the sera of Groups II and IV; while those of Group IV are not agglutinated by the serum of any of the other three groups.

Second Reaction. The serum of Group I agglutinates no other corpuscles; that of Group II agglutinates the corpuscles of Groups I and III; that of Group III agglutinates the corpuscles of Groups I and II; and the serum of Group IV agglutinates the corpuscles of Groups I, II and III.

These results are set out in Table I.

TABLE I. INTERACTION OF BLOOD GROUPS.

Corpuscles.	Serum.			
	Group I.	Group II.	Group III.	Group IV.
Group I ...	—	+	+	+
Group II ...	—	—	+	+
Group III ...	—	+	—	+
Group IV ...	—	—	—	—

+ = agglutination.
— = no agglutination.

Agglutinins and Iso-agglutinins. The active principles in the serum have been named agglutinin and hæmolysin; and those in the corpuscles iso-agglutinin and iso-hæmolysin. A positive reaction (agglutination or

hæmolysis) depends on the presence and interaction of these substances in the serum and corpuscles of the two bloods which are being grouped. For example, the serum of Group I lacks agglutinins and the corpuscles of Group IV have no iso-agglutinins (see Table I), therefore the serum of Group I cannot agglutinate the corpuscles of any group, and the corpuscles of Group IV are not agglutinated by the serum of any group; thus individuals belonging to Group I are "universal recipients," and those belonging to Group IV are "universal donors."

Blood Groups of Children.

It has been stated that an infant has no blood group, and that a baby's blood is compatible with that of its mother. As blood transfusion is so common and successful a form of treatment in burns, surgical shock, marasmus, malæna neonatorum, etc., it is of vital importance to know whether these statements are true or false.

That they are false has been fully proved by Keynes[4] and Happ[5]. The former grouped a series of newly-born infants, and got many well-marked agglutinations among them, thus proving the existence of definite Groups I, II and III, as the case might be.

In 1920 Happ published the results of his work on blood reactions in children. He found, first, that blood from the umbilical cord often belonged to a different group from that of the maternal blood; and secondly that, although the agglutination reaction of the serum (agglutinins) may not be established until the child is a few months or even two years old, the reaction in the corpuscles (iso-agglutinins) appears before that of the serum, and is often present at birth. If the grouping which first appears (at birth) is modified in later life, it is always by the addition of factors—thus a Group IV may develop agglutinins or iso-agglutinins, or both, and so become a Group II or III; Groups II and III may become Group I, and so on. The reactions, however, are completely established within the first two years of life.

Happ therefore concludes that it is unsafe to transfuse an infant with its mother's blood without first making the usual tests, not only because the child may not belong to the same group as the mother, but also because, although the child's serum may still be without agglutinins, the iso-agglutinins may be already present, and thus transfusion might have serious results if the donor's blood were of an incompatible group.

Keynes has experimentally proved that blood groups are inherited on a definite plan, that of the Mendelian law.

Present Series of Children and Infants.

The following analysis of two hundred children corroborates the investigations of Keynes[4] and Happ[5].

The first hundred children examined were all under the age of twelve. They were normal boys and girls suffering from incidental surgical complaints, such as hernia, genuvarum, etc. The second hundred were infants under one year, most of whom were suffering from pneumonia, diarrhœa, vomiting, etc. None had any disease of the blood in which abnormal alteration of blood reactions is known to occur (Keynes).

The results obtained in both series, children and infants, are shown in Table II, where percentages found in large series of adults are also set out for the sake of comparison. It will be seen that the percentages obtained in both of the present series approximate to those found in adults.

TABLE II. Blood Groups in Children and Infants.

	Author's Series.		Moss.	Culpepper.
	100 Children.	100 Infants.	1,600 Adults.	5,000 Adults.
Group I ...	6%	1%	10%	3%
Group II ...	39%	36%	40%	38%
Group III ...	9%	6%	7%	18%
Group IV ...	46%	57%	43%	41%

Conclusions.

1. Infants as well as children have a definite blood group.

2. In infants Group I contains a smaller, and Group IV a larger, proportion of cases than in children. This suggests that the blood groups may not be established during the early months of life.

3. Sex and colouring had no apparent relationship to the blood groups.

I am indebted to Prof. John Fraser for the suggestion that I should undertake this investigation, and for granting me facilities in his wards at the Royal Hospital for Sick Children, Edinburgh.

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THE BRITISH PÆDIATRIC ASSOCIATION.

The first Meeting of the British Pædiatric Association will take place at Windermere on May 4th and 5th. Dr. G. F. Still will preside. For some time the need has been felt for an association which would attract pædiatric physicians from every part of the British Isles. The rules and conduct of business are based on those of the Association of Physicians. The objects are the advancement of the study of pædiatrics and the promotion of friendship among pædiatricians. The response to the invitations issued has been so unanimous and the list of communications promised for this year so large and interesting, that the success of this first Meeting is assured. It is intended, with the consent of the Association, to publish a brief résumé of the proceedings in the June number of the "Archives."